Indian J. Chem., Vol. 26B No. 8 pp. 707-808
August 1987
CODEN : IJOCAP ISSN : 0019-5103
26B(8) 707-808 (1987)



# Indian Journal of
# CHEMISTRY

**SECTION B**
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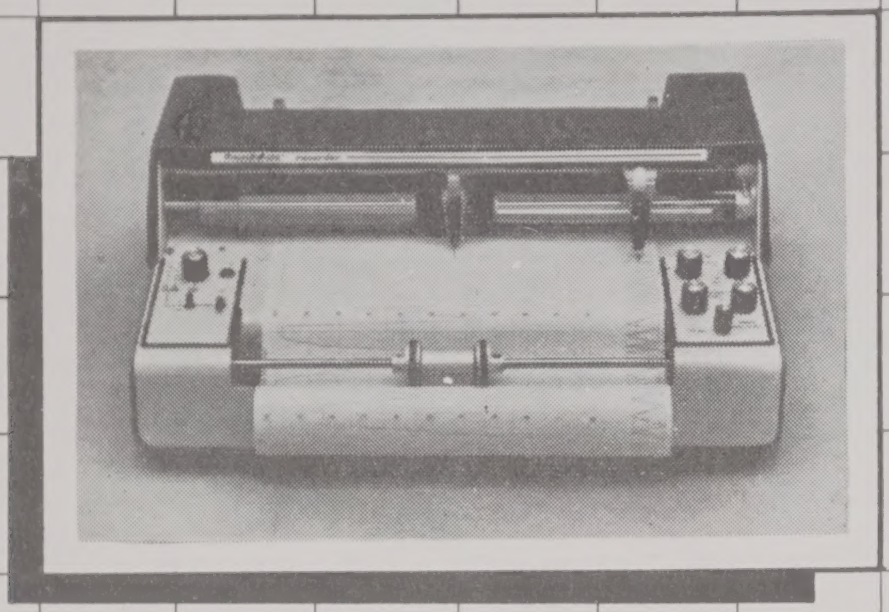

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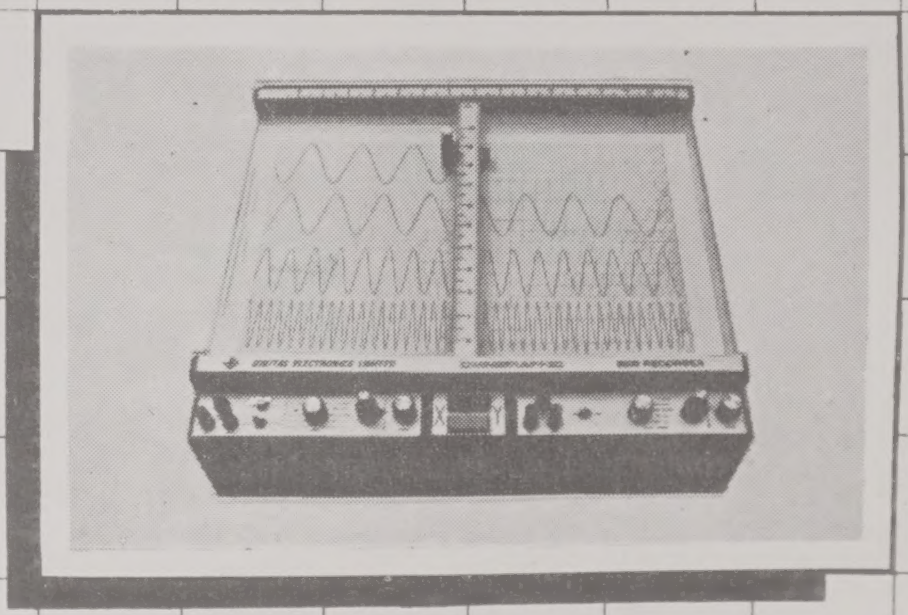

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## Section B: Organic Chemistry including Medicinal Chemistry




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The Indian Journal of Chemistry is issued monthly in two sections: A and B. Communications regarding contributions for publication in the journal should be addressed to the Editor, Indian Journal of Chemistry, Publications & Information Directorate, Hillside Road, New Delhi 110 012.

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# Indian Journal of Chemistry

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Authors for correspondence are indicated by (*)

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*Communications*

# Synthesis of Di- & Tetra-thiaparacyclophanes Under Phase Transfer Conditions

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*Received* 1 *June* 1987; *accepted* 10 *July* 1987

Di- and tetra-thiaparacyclophanes (**3**) and (**4**) respectively, have been synthesised using *p*-xylene dibromide (**1**) and appropriate dithiol generated *in situ* from dithiouronium salts (**2**) under liquid-liquid or solid-liquid phase transfer conditions.

Synthesis of symmetrical[1] and unsymmetrical[2] thioethers from thioiminium salts as source of thiolate ions, and organic halides has been reported under phase transfer (PT) conditions. Thiacyclophanes have been synthesised so far through a variety of cumbersome, multistep procedures which suffer from many drawbacks, viz. relatively poor yields, longer reaction time and forcing conditions[3,4]. Synthesis of cyclophanes under PT conditions does not appear to have been tried so far[3,4]. Herein we report the synthesis of the title compounds under PT conditions using dithiouronium salts (**2**) as source for *in situ* generation of dithiols, and *p*-xylene dibromide (**1**) as an organic dihalide.

In a typical experiment a mixture containing equivalent amounts of dithiouronium salt (**2**) and *p*-xylene dibromide (**1**) in benzene, 50% aq NaOH as base the triethylbenzylammonium chloride (TEBA) was refluxed for appropriate time (Table 1). After completion of the reaction (TLC), the two-component reaction mixture was worked up and chromatographed to give the products **3** and **4** (Table 1).

The first component was assigned the structure as 2,6-dithia[7]paracyclophane (**3**, $n=3$) and the second component as 2, 6, 15, 19-tetrathia[7, 7′]paracyclophane (**4**, $n=3$) on the basis of their spectral and analytical data. The identity was finally confirmed by direct comparison with authentic samples[5].

Recently solid-liquid PTC has been preferred over liquid-liquid PTC in performing a variety of reactions[6]. Thus, in the present reactions also better yields were obtained under solid-liquid PTC and the reaction time was also considerably reduced (Table1).

The experiment under solid-liquid PTC was performed as follows:

A mixture containing equivalent amounts of **1**

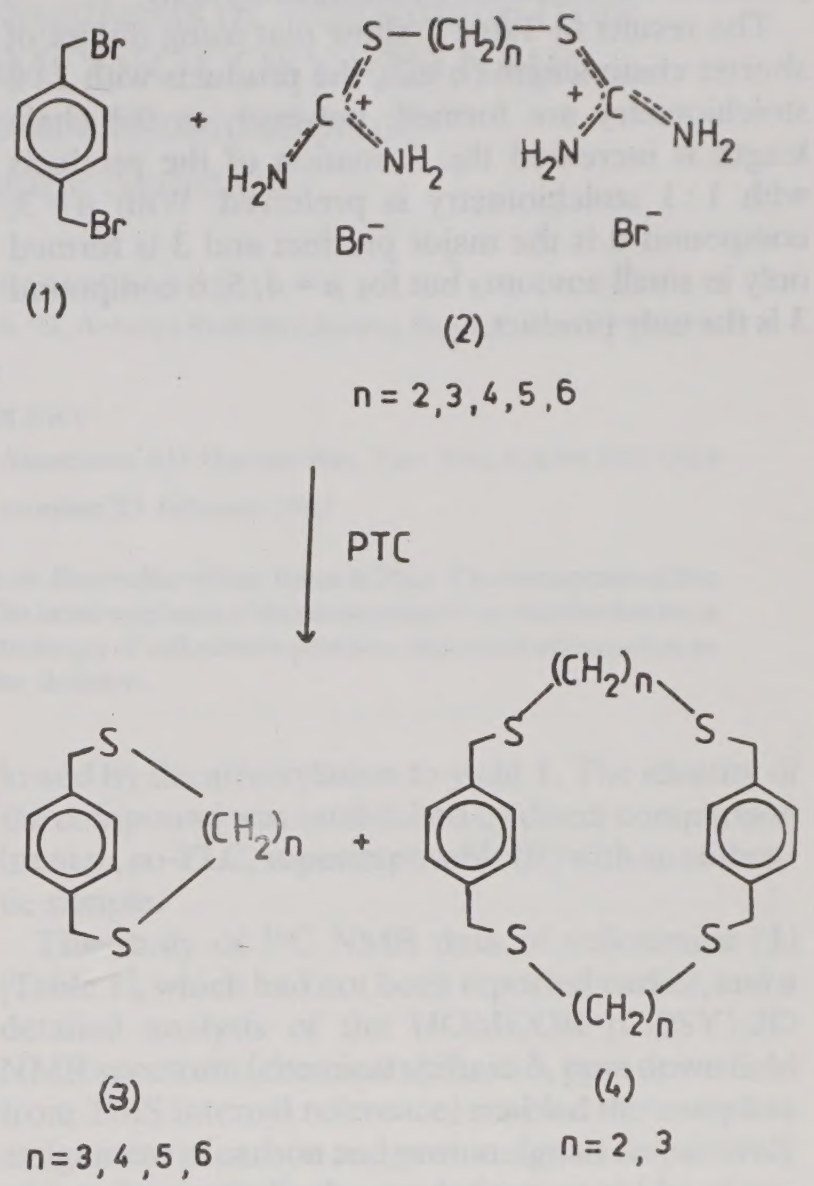


Table 1—Formation of Di- and Tetra-thiaparacyclophanes (**3** and **4**)[a,b]

| Sl No. | *n* | Time (hr) | Yield (%) | | m.p. (°C) | ($M^+$) *m/z* |
|---|---|---|---|---|---|---|
| | | | **3** | **4** | | |
| 1 | 2 | 12(8)[c] | — | 10(12)[c] | | |
| 2 | 3 | 12(6-7) | 8 | 14(25) | | |
| 3 | 4 | 8(6) | 45(65) | — | 72 | 224 |
| 4 | 5 | 8(4) | 55(60) | — | 79 | 238 |
| 5 | 6 | 4(4) | 60(75) | — | 42 | 252 |

(a) PMR of compounds:
(i) **4** ($n=2$): $\delta$ 3.56 (*s*, 8H, $-SCH_2$), 3.66 (*s*, 8H, $-SCH_2Ph$), 7.3 (*m*, 8H, ArH)
(ii) **3** ($n=4$): $\delta$ ≮ ≠ ≥ ⊂ *m*, 4H, $-CH_2$), 2.2 (*m*, 4H, $-SCH_2$), 3.5 (*s*, 4H$_2$ $-SCH_2Ph$), 7.0 (*m*, 4H, ArH)
(iii) **3** ($n=5$): $\delta$ 1.5 (*m*, 6H, $-CH_2$), 2.3 (*m*, 4H, $-SCH_2$), 3.5 (*s*, 4H, $-SCH_2Ph$), 7.1 (*m*, 4H, ArH).
(iv) **3** ($n=6$): $\delta$ 1.1 (*m*, 8H, $-CH_2$), 2.1 (*m*, 4H, $-SCH_2$), 3.5 (*s*, 4H, $-SCH_2Ph$), 7.0 (*m*, 4H, ArH).
(b) All these compounds gave satisfactory analytical data.
(c) Figures in parentheses indicate the yields and reaction time under solid-liquid PTC.

and **2** in benzene, fused pulverised KOH as base and TEBA as catalyst was refluxed for the time period given in Table 1. After the usual work up, the products were isolated by chromatography.

The results in Table 1 show that using dithiol of shorter chain length ($n=2$), the products with 2 : 2 stoichiometry are formed; however, as the chain length is increased the formation of the products with 1 : 1 stoichiometry is preferred. With $n=3$, compound **4** is the major product and **3** is formed only in small amounts but for $n=4, 5, 6$ compound **3** is the only product.

Miss Anupa Jain thanks the UGC, New Delhi for financial assistance.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 709-711



# Studies on Apocynaceae: Hemi-Synthesis of Vellosimine from Rhazine—Application of HOMCOR (COSY)-2D NMR Spectroscopy in Structure Elucidation of Ajmaline-Sarpagine Skeleton

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*Received* 26 *December* 1986; *accepted* 23 *February* 1987

The rare indole alkaloid vellosimine (**1**) has been isolated from *Rauwolfia reflexa* Teism & Binn. The occurrence of this indolic base has been observed for the first time in *R. reflexa*. The hemi-synthesis of this compound from rhazine has been achieved. The study of the HOMCOR (COSY)-2D NMR spectroscopy of vellosimine provides important information on structure elucidation of the alkaloids having ajmaline-sarpagine skeleton.

A rare ajmaline-sarpagine type alkaloid vellosimine (**1**) has been isolated from the leaves of *Rauwolfia reflexa* Teism and Binn (Apocynaceae). The hemi-synthesis of the compound was achieved from rhazine (**2**)[1,2], major constituent of *Alstonia scholaris* R Br (Chart 1).

Rhazine (**2**) on careful oxidation with pyridinium chlorochromate (PCC) in dry methylene chloride afforded the aldehyde (**3**), $C_{21}H_{22}N_2O_3$ ($M^+$ 350), m.p. 230° (chloroform); IR; 1720 (—CHO) and 1735 $cm^{-1}$ (—$CO_2Me$). That the oxidation of the hydroxymethyl group in (**2** had occurred was further confirmed by the appearance of the aldehydic prolin as a sharp singlet at δ9.68 in the PMR spectron of **3**. Treatment of **3** with 2**N** methanolic potassium hydroxide at 30° (6 hr) followed by warming at 90° (10 min) resulted in hydrolysis of carbomethoxy group at C-16 followed by decarboxylation to yield **1**. The identity of the compound was established by direct comparison (m.m.p., co-TLC, superimposable IR) with an authentic sample.

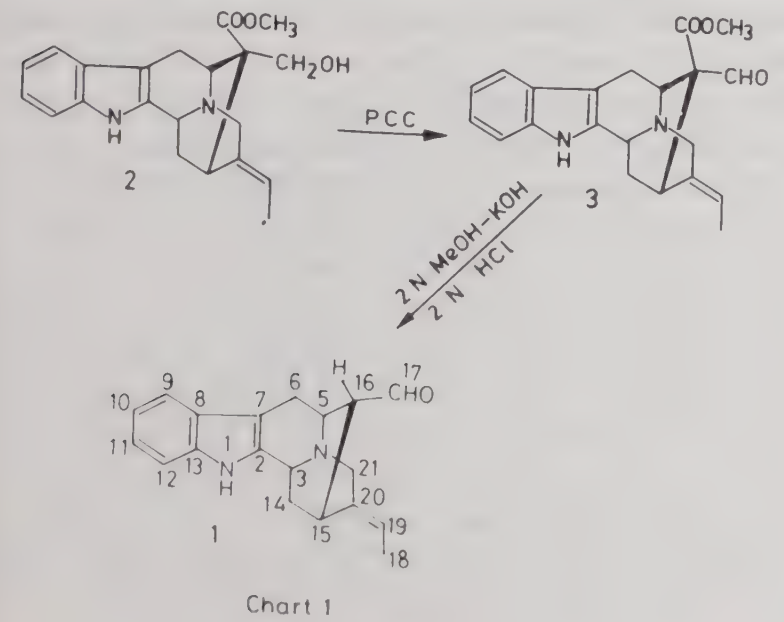


Chart 1

The study of $^{13}C$ NMR data of vellosimine (**1**) (Table 1), which had not been reported earlier, and a detailed analysis of the HOMCOR (COSY)-2D NMR spectrum (chemical shifts in δ, ppm down field from TMS internal reference) enabled the complete assignment of carbon and proton signals respectively of **1** to be made. Such correlations would be of importance in the structure determination of unknown alkaloids having similar ajmaline-sarpagine skeleton.

The HOMCOR (COSY) − 2D NMR spectrum (Fig. 1) clearly demonstrated that the proton at 5.25 (1H, *q*, with finer splitting, $J = 7.0$ Hz) coupled to the methyl group at 1.55 (3H, *d*, with finer splitting,

Table 1—100 MHz $^{13}C$ NMR Signals of Vellosimine (**1**) in $CDCl_3$

| Carbon Number | Chemical shift (in ppm) | Carbon Number | Chemical shift (in ppm) |
|---|---|---|---|
| 2 | 135.99 | 13 | 135.16 |
| 3 | 53.82 | 14 | 31.94 |
| 5 | 50.47 | 15 | 26.00 |
| 6 | 25.85 | 16 | 50.30 |
| 7 | 102.88 | 19 | 118.24 |
| 8 | 130.24 | 20 | 126.40 |
| 9 | 119.15 | 21 | 54.66 |
| 10 | 121.55 | $-CH_3$ | 12.14 |
| 11 | 117.60 | −CHO | 200.00 |
| 12 | 110.89 | | |

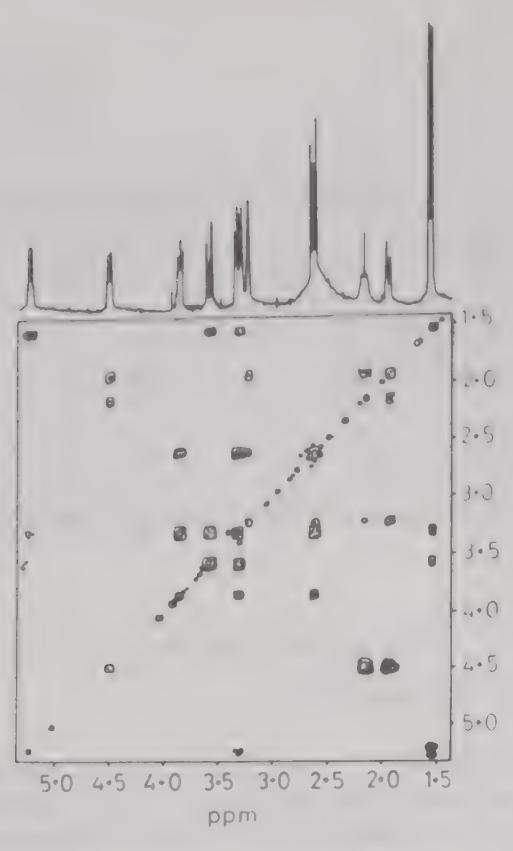


Fig. 1 – Homonuclear correlation plot (COSY) of vellosimine (**1**)

$J$ = 7.0 Hz) indicating an ethylidene group. The presence of three $sp^3$ $CH_2$ and four $sp^3$ CH protons could also be ascertained. The methyl protons at 1.55 and the olefinic protons at 5.25 were allylic to $CH_2$ protons at 3.35 and 3.60. These methylene protons are coupled to each other ($J$ = 15.0 Hz) and represent the protons at C-21. The other proton at 3.35 appeared as a doublet of doublets ($J$ = 15.0 and 5.0 Hz) and was in fact part of another non-equivalent methylene pair, appearing at 2.65 ($J$ = 15.0 and 3.0 Hz). These two protons are therefore correctly assigned to the protons at C-14 and were involved in coupling to the $sp^3$ CH proton at C-3 (3.85, *dd*, $J$ = 5.0 and 3.0 Hz). The third $CH_2$-pair at C-6 could be clearly seen at 1.95 (*d*, with finer splitting, $J$ = 12.0 Hz) and 2.15 (ill-resolved). The latter coupled with the $sp^3$CH at C-5 (δ4.50, *d*, with finer splitting, $J$ = 8.0 Hz). One of the C-6 protons at δ1.95 also showed a long range coupling with the $sp^3$ CH proton at C-16 (3.22, 1H, *bs*).This observation confirmed that the —CHO group at C-16 must be situated away from the aromatic nucleus. The proton at C-16 must be situated away from the aromatic nucleus. The proton at C-16 also showed a coupling with the C-15 proton which appeared at 2.60 (1H, *bs*). All the signals for the protons of vellosimine (**1**) could therefore be correlated and clearly explained.

## Experimental Procedure

Melting points were recorded on Kofler block apparatus and are uncorrected. The UV spectra (in 95% aldehyde-free ethanol) were recorded on a Varian 634 spectrophotometer, IR spectra (in KBr) on a Perkin-Elmer 782 spectrophotometer, 40 MHz PMR spectra (in $CDCl_3$ using TMS as the internal standard), $^{13}C$ NMR spectra (in $CDCl_3$) on a Varian XL-400 spectrometer and the mass spectra at 70 eV on a Hitachi RMU 6L mass spectrometer.

### *Isolation of vellosimine* (**1**)

The air-dried and powdered leaves of *Rauwolfia reflexa* Teism and Binn (2.5 kg) were percolated with methanol at 25° for 21 days. The extract was concentrated, churned with 5% citric acid for 20 hr and filtered. The filtrate was basified with liquor ammonia ( *p*H 10) and the liberated base was extracted with benzene (5 × 300 ml) and the organic layer was made ammonia-free by repeated washing with water (5 × 200 ml) and dried. The benzene concentrate was chromatographed over basic alumina (BDH, 60-120 mesh), Vellosimine (**1**) was isolated from the benzene eluent and crystallised from chloroform m.p. 260°, yield 25 mg (0.001%) (Found: C, 77.2; H, 6.2; N, 10.1. $C_{19}H_{20}N_2O$ requites C, 78.1; H, 6.8; N, 9.6%); UV: 226 (log ε 4.52), 283 (3.82) and 300 nm (3.00); IR: 3400, 1710, 1625, 1500, 1470, 1450, 750 $cm^{-1}$; PMR: 9.60 ( − CHO),. 9.08 ( > NH), 7.60-7.00 (m, Ar-H), 5.25 (1H, *q*, $J$ = 7.0 Hz, $C_{19} - H$), 3.85 (1H, *dd*, $J$ = 5.0 and 3.0 Hz, $C_3$-H), 1.55 (3H, *d*, $J$ = 7.0 Hz, $-CH_3$); MS: 292 (M), 291, 263, 249, 182, 169, 168.

### *Reaction of rhazine* (**2**) *with pyridinium chlorochromate* (*PCC*)

To a well stirred solution of pyridinium chlorochromate (PCC) (100 mg) in dry methylene chloride (20 ml) rhazine (**2**, 100 mg) in dry methylene chloride (10 ml) was added at 25°, Stirring was continued for 1.5 hr. Methylene chloride (100 ml) was added and the supernatant liquid decanted. The black gum was wshed with methylene chloride (5 × 20 ml), the combined methylene chloride extract filtered, concentrated and the concentrate chromatographed over silica gel. Compound (**3**) was obtained as a while solid from benzene-ethyl acetate (9:1) m.p. 230° (chloroform), yield 50 mg (50%) (Found: C, 71.8; H, 6.6: N, 7.5. $C_{21}H_{22}N_2O_3$ requires C, 72.0; H, 6.3; N, 8.0%); UV: 226 (log ε 4.50), 282 (3.67) and 290 nm (3.65); IR: 3400, 1735, 1720, 1650, 1620, 1605, 1445, 1260, 750 $cm^{-1}$; PMR: 9.68 ( − CHO), 8.72 ( > NH), 7.20-6.86 (*m*, Ar-H), 5.12 (1H, *q*, $J$ = 7.0 Hz, $C_{19} - H$), 3.95 (1H, *dd*, $J$ = 5.0 and 3.0 Hz, $C_3 - H$), 3.62 (—$COOCH_3$) 1.60 (3H, *d*, $J$ = 7.0 Hz, $-CH_3$); MS: 350 ($M^+$), 349, 306, 291, 263, 223, 184, 156, 128.

*Transformation of* **3** *to vellosimine* (**1**)

To compound (**3**, 40 mg) 2N methanolic potassium hydroxide solution (30 ml) was added and kept at 30° for 6 hr. The mixture was acidified with 2N hydrochloric acid (30 ml) and warmed for 10 min on a water-bath. The mixture was diluted with water (100 ml) and neutralised with 2% aq sodium bicarbonate. It was extracted with chloroform (3 × 50 ml), washed with water (3 × 30 ml) and dried. Concentration of the solution afforded vellosimine (**1**), which was crystallised from chloroform, m.p. 260°, yield 22 mg (55%); IR: 3400, 1710, 1625, 1500, 1470, 1450, 750 $cm^{-1}$.

**Acknowledgement**

The authors thank Mr A Acharya, Mr J Ghose and Mr P Ghosh of the Organic Instrumentation Laboratory, Calcutta University and Dr S C Pakrashi, Director, Indian Institute of Chemical Biology, Calcutta, for spectral measurements and to the DST, New Delhi for financial assistance.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 712-714

# Synthesis of 4-Oxypterosin-E, a New Phenolic Indanone Norsesquiterpene†

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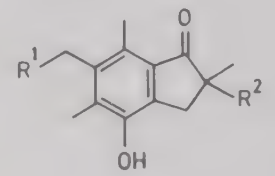
*Received* 24 *December* 1986; *accepted* 28 *January* 1987

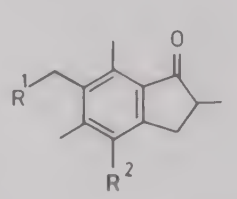
The synthesis of 4-oxypterosin E (**6**), a phenolic indanone norsesquiterpene, is described. The synthesis starts from an ester-ether derivative (**9**) of the known 3-hydroxy-2,6-dimethyl-1-phenylacetic acid (**8**) and involves formylation, Horner reaction, hydrolysis, hydrogenation, cyclodehydration and demethylation in succession, as depicted by the sequence: **9** → **10** → **11** → **12** → **13** → **14** → **6.**

The pterosins belong to a growing family of naturally occurring sesqui- and norsesqui-terpenoid indanones[1] and their interesting biogeneses and biological properties have attracted the attention of synthetic organic chemists[2]. Among these, five are phenolic pterosins, pterosin-M[3] (**1**), pteroside-M[3] (**2**), onitin[4,5] (**3**), onitisin[4] (**4**) and pterosin-R[5] (**5**). In this paper is reported the synthesis of a new phenolic analogue, 4-oxypterosin-E (**6**), of the naturally occurring pterosin-E[6] (**7**).

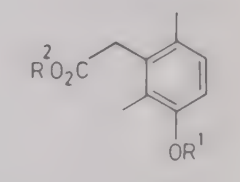
The starting material, 3-hydroxy-2,6-dimethyl-1-phenylacetic acid (**8**) has earlier been prepared in this laboratory[7] as a synthon for quassin. Treatment of ether-ester derivative (**9**) of **8** with hexamine in trifluoroacetic acid[8] led to the aldehyde (**10**) in 67% yield. Horner reaction[9] on **10** with methyl 2-(diethylphosphono)propionate gave the carbomethoxymethylcinnamate (**11**), the E/L ratio of which was not determined, as the double bond was anyway reduced in the next step. On hydrolysis it gave the dicarboxylic acid (**12**). The ethylenic double bond of **12** was reduced by lithium in liquid ammonia[10] and the resulting saturated dicarboxylic acid (**13**) on cyclodehydration with polyphosphoric acid gave the indanone (**14**) in 38% yield which was improved to 80% by the use of anhydrous hydrofluoric acid[11]. Demethylation of **14** with hydrobromic in acetic acid[12] led to 4-oxypterosin-E (**6**).



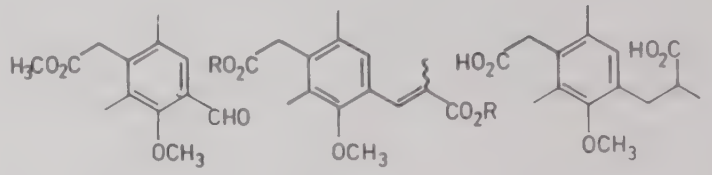
1, $R^1 = CH_2OH$; $R^2 = H$
2, $R^1 = CH_2OGlu$; $R^2 = H$
3, $R^1 = CH_2OH$; $R^2 = CH_3$
4, $R^1 = CH_2OH$; $R^2 = CH_2OH$
5, $R^1 = CH_2Cl$; $R^2 = CH_3$



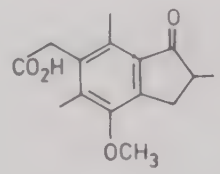
6, $R^1 = CO_2H$; $R^2 = OH$
7, $R^1 = CO_2H$; $R^2 = H$



8, $R^1 = R^2 = H$
9, $R^1 = R^2 = CH_3$



10 | 11, R = $CH_3$; 12, R = H | 13



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## Experimental Procedure

Melting points are uncorrected. PMR spectra were recorded on a Varian T-60 instrument with TMS as internal standard (chemical shifts in δ ppm) and IR spectra (νmax in $cm^{-1}$) on Perkin-Elmer 397, 599 and 781 spectrophotometers. Bath temperature (b.t.) pertains to evaporative short-path distillations. By extractive work-up is meant the standard sequence: exhaustive solvent extraction of the product/s of a reaction, appropriate washing of the combined organic phase, drying (anhyd. $Na_2SO_4$) and removal of the solvent to the last trace from the dried extract.

*Methyl* 2,6-*dimethyl*-3-*methoxy*-1-*phenylacetate* (**9**)

A mixture of **8**[7] (21.6 g, 0.12 mol), anhyd. $K_2CO_3$ (41.4 g), dimethyl sulphate (31.5 g) and dry acetone (500 ml) was heated to reflux for 24 hr. Most of the acetone was removed *in vacuo*, and water (500 ml) added to the residue. Extractive work-up of the neutral product gave **9** (22 g); yield 88%. An analytical sample was obtained by preparative TLC ($SiO_2$, hexane-ethyl acetate); b.t. 145°/1 mm; IR (film): 1730 (C=O), 1600, 1590 (aromatic); PMR ($CCl_4$): 2.1 (3H, *s*, Ar-$CH_3$), 2.2 (3H, *s*, Ar-$CH_3$), 3.5 (5H, *s*, $OCH_3$, Ar-$CH_2CO_2CH_3$), 3.63 (3H, *s*, $OCH_3$), 6.43 (1H, *d*, *J*=8 Hz, Ar-$H_4$), 6.76 (1H, *d*, *J*=8 Hz, Ar-

†Part LXXIX in the series, Studies in Terpenoids.
Part LXXVIII, see ref. 7.

$H_5$) (Found: C, 69.0; H, 7.4. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%).

*Methyl* 2,6-*dimethyl*-4-*formyl*-3-*methoxy*-1-*phenylacetate* (**10**)

A mixture of **9** (2.08 g, 10 mmol), hexamine (1.97 g, 13 mmol) and $F_3CCO_2H$ (20 ml) was heated to reflux for 12 hr. The reaction mixture was cooled and poured onto excess of water (100 ml) and neutralized by the addition of $K_2CO_3$. Extractive work-up, followed by column chromatography ($SiO_2$, benzene) gave **10** (1.6 g); yield 67%; b.t. 125°/1.5 mm; IR (film): 1730 (ester C=O), 1680 (H−C=O), 1590 (aromatic); PMR ($CCl_4$): 2.23 (3H, *s*, Ar-$CH_3$), 2.26 (3H, *s*, Ar-$CH_3$), 3.63 (5H, *s*, .$OCH_3$, AR-C$H_2CO_2CH_3$), 3.73 (3H, *s*, $OCH_3$), 7.33 (1H, *s*, Ar-H), 10.2 (1H, *s*, CHO) (Found: C, 65.9; H, 6.6. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%).

*Methyl* 4-*carbomethoxymethyl*-2-*methoxy*-2′-3,5-*trimethylcinnamate* (**11**)

To a slurry of NaH (0.2 g, 8 mmol, freed from mineral oil) in dry THF (10 ml) at room temperature a solution of methyl 2-(diethylphosphono)propionate (8 mmol) (prepared from methyl α-bromopropionate) in THF (5 ml) was added under vigorous stirring. To the reaction mixture after cooling, **10** was added in one portion and the stirring continued overnight. Most of the solvent was removed *in vacuo* and water (50 ml) added. Extractive work-up gave **11** (1.8 g); yield 84%. Preparative TLC gave an analytical sample, b.t. 150°/1.5 mm; IR (film): 1710 (unsaturated ester C=O), 1730 (saturated ester C=O); PMR ($CCl_4$): 2.0 (3H, *d*, *J*=2 Hz, C=C−$CH_3$), 2.2 (3H, *s*, Ar-$CH_3$), 2.26 (3H, *s*, Ar-$CH_3$), 3.53 (2H, *s*, AR-C$H_2CO_2CH_3$), 3.56 (3H, *s*, $OCH_3$), 3.6 (3H, *s*, $OCH_3$), 3.73 (3H, *s*, $OCH_3$), 6.86 (1H, *s*, Ar-H), 7.6 (1H, *bs*, CH=C) (Found: C, 66.2; H, 7.0. $C_{17}H_{22}O_5$ requires C, 66.7; H, 7.2%).

4-*Carboxymethyl*-2-*methoxy*-2′,3,5-*trimethylcinnamic acid* (**12**)

A mixture of **11** (1.5 g, 5 mmol) in ethanol (20 ml) and aq. NaOH (20 ml, 10%) was heated to reflux for 12 hr. Most of the volatiles were removed *in vacuo* and the residue neutralized with dil. HCl. The separated solid was filtered and dried to give **12** (1.2 g); yield 86%; m.p. 238° (methanol); IR (nujol): 2200-3300 (O=COH, br), 1690 (C=O); PMR ($CDCl_3$): 2.0 (3H, *d*, *J*=2 Hz, C=C−$CH_3$), 2.2 (3H, *s*, Ar-$CH_3$), 2.26 (3H, *s*, Ar-$CH_3$), 3.56 (5H, *s*, $OCH_3$ and Ar-C$H_2CO_2H$), 6.96 (1H, *s*, Ar-H), 7.66 (1H, *bs*, −C=CH), 8.36 (2H, *bs*, 2×$CO_2H$) (Found: C, 65.1; H, 6.7. $C_{15}H_{18}O_5$ requires C, 64.7; H, 6.5%).

4-*Carboxymethyl*-2-*methoxy*-2′,3,5-*trimethyldihydrocinnamic acid* (**13**)

To distilled liquid $NH_3$ (150 ml) a solution of **12** (1.1 g, 4 mmol) in dry THF (10 ml) was added under stirring followed by pieces of lithium (200 mg), when the colour of the solution became blue. After stirring for 1 hr, the reaction was quenched by the slow addition of solid $NH_4Cl$ till the colour got discharged. Ammonia was allowed to evaporate and the residue taken in water (50 ml) and neutralized with conc. HCl. Extractive work-up gave **13** (0.9 g); yield 80%. Preparative TLC gave an analytical sample as a viscous liquid; IR (nujol): 2200-3650 (O=C*OH*), 1700 (C=O), PMR ($CDCl_3$): 1.3 (3H, *bd*, CHC$H_3$), 2.2 (6H, *s*, 2×Ar-$CH_3$), 2.43-3.26 (3H, *m*, C*H*$CH_3$, Ar-C$H_2$-CH), 3.6 (5H, *s*, $OCH_3$, Ar-C$H_2CO_2H$), 6.8 (1H, *s*, Ar-H), 11.8 (2H, *bs*, 2×$CO_2H$) (Found: C, 64.2; H, 7.1. $C_{15}H_{20}O_5$ requires C, 64.3; H, 7.2%).

6-*Carboxymethyl*-4-*methoxy*-2,5,7-*trimethylindan*-1-*one* (**14**): (*i*) *By cyclodehydration with polyphosphoric acid* (*PPA*)

A mixture of **13** (0.28 g, 1 mmol) and PPA [prepared from $P_2O_5$ (15 g) and $H_3PO_4$ (10 ml)] was stirred vigorously for 4 hr at 100°. The reaction mixture was poured onto crushed ice (50 g) and water (25 ml). Extractive work-up after standing overnight, followed by purification by preparative TLC afforded an analytically pure sample of **14** as a viscous liquid (0.1 g); yield 38%; IR (nujol): 2500-3600 (O=C−OH), 1700 (C=O), 1590 (aromatic); PMR ($CDCl_3$): 1.26 (3H, *d*, *J*=8 Hz, CHC$H_3$), 2.33 (3H, *s*, Ar-$CH_3$), 2.46-2.83 (2H, *m*, Ar-C$H_2$CH), 2.63 (3H, *s*, Ar-$CH_3$ *peri* to C=O), 3.3 (1H, *m*, C*H*$CH_3$), 3.83 (5H, *s*, $OCH_3$, Ar-C$H_2CO_2H$), 9.8 (1H, *bs*, $CO_2H$, exchangeable with $D_2O$) (Found: C, 68.8; H, 7.0. $C_{15}H_{15}O_4$ requires C, 68.7; H, 6.9%).

(*ii*) *By cyclodehydration with anhyd HF*

To distilled anhyd. HF (100 ml) in a plastic container, **13** (0.56 g, 2 mmol) was added under stirring at 10° and the stirring continued for 6 hr. After allowing HF to evaporate, the residue was treated with water (100 ml). The usual extractive work-up gave **14**, identical with the above sample (0.42 g); yield 80%.

6-*Carboxymethyl*-4-*hydroxy*-2,5,7-*trimethylindan*-1-*one* (4-*oxypterosin-E*) (**6**)

A solution of **14** (0.52 g, 2 mmol) in gl. acetic acid (8 ml) and HBr (48%, 6 ml) was heated for 4 hr at 100°. Most of the acetic acid was removed *in vacuo*. Extractive work-up of the residue after dilution with water, followed by chromatographic purifica-

tion (silica gel column; ethyl acetate-benzene, 1:1) of the product afforded **6** (0.35 g); yield 70%, m.p. 204° (acetone-benzene); IR (nujol): 2500-3500 (*OH*, O=C−OH), 1690 (C=O), 1610, 1590 (aromatic); PMR (DMSO-$d_6$): 1.26 (3H, *d*, *J*= 8 Hz, CHC*H*$_3$), 2.3 (3H, *s*, Ar-C*H*$_3$), 2.46-2.9 (2H, *m*, Ar-C*H*$_2$CH), 2.56 (3H, *s*, Ar-C*H*$_3$ *peri* to C=O), 2.96-3.46 (1H, *m*, C*H*CH$_3$), 3.7 (2H, *s*, ArC*H*$_2$CO$_2$H), 4.63 (2H, *bs*, OH and $CO_2H$, exchangeable with $D_2O$) (Found: C, 68.0; H, 6.6. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5%).

**Acknowledgement**

The authors thank the CSIR, New Delhi, for finacial assistance and for the award of a senior research fellowship to one of them (BR).

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 715-721

# Triterpene Glycosides & Aglycones of Sea Cucumbers *Holothuria atra* & *H. scabra* (Holothurideae)

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*Received* 13 *October* 1986; *accepted* 10 *December* 1986

From the acid hydrolysates of the methanol extracts of the sea cucumbers *Holothuria atra* and *H. scabra* (phylum: echinodermata; fam:Holothurideae) collected at Mandapam coast (Tamil Nadu), a total of nine *Holothuria* sapogenins (compounds A-G, L and M) and two glycosides (H and K) have been isolated by column chromatography and characterised by spectral (UV, IR, PMR and mass) data. Compound C is established as the novel 11-keto-9(11)-dihydro-22, 25-oxidoholothurinogenin (III). Compound D (isolated as acetate) is the new 3$\beta$-acetoxy-12$\beta$-methoxy-7, 8-dihydroholothurinogenin (IVa). Compounds F and G (isolated as acetates) are identified as 3$\beta$, 12$\alpha$-diacetoxy-7, 8-dihydro-holothurinogenin (VIa) and 3$\beta$, 12$\alpha$-diacetoxy-7, 8-dihydro-22, 25-oxidoholothurinogenin (VIIa) respectively. For the first time, these two genuine aglycones have been isolated as survivors of acid hydrolysis. glycoside H is identified as the unique 3-O-( $\beta$ – D – xylopyranosyl)-22, 25-oxidoholothurinogenin (VIII). The remaining six compounds (A, B, E, L, M and glycoside K) are all known compounds; however these are reported for the first time from *H.* atra and *H. scabra* (except compound A in both and compound B in *H. atra*).

The sea cucumbers (phylum: echinodermata) are of wide occurrence in the intertidal regions of tropical as well as sub-tropical seas. They contain toxic saponins[1] for their chemical defence against predators. Neurotoxicity and antifungal activity have been attributed to them, the latter providing a potential application in the cure of superficial dermatophytosis[2]. So far, about 50 aglycones and 25 glycosides, all based on 20*S*-hydroxy-5$\alpha$-lanostane have been reported. Among the 50 and odd species so far subjected to chemical investigations, *Holothuria* species (fam:Holothurideae) are the most studied because of their prolific occurrence[3]. In spite of this world-wide interest on these organisms, no chemical work has so far been reported on sea cucumbers of Indian origin and hence the title investigation.

We have earlier shown[4] that the chemical composition of the same marine species might vary depending on the ecological status of the habitat and the particular variety of the organism. Corroborating this premise, we describe in this paper, the isolation and characterisation of a total of nine *Holothuria* sapogenins of sea cucumbers *Holothuria atra* and *H. scabra* collected in large numbers from Mandapam Camp, Tamil Nadu. Of the nine sapogenins III is a novel 11-ketoaglycone, and IV, a new 12$\beta$-O-methyl ether. For the first time, the genuine aglycones, VI and VII are isolated as survivors of acid hydrolysis. The remaining five sapogenins are known compounds. Further, two glycosides are reported of which VIII is an unprecedented xyloside of holothurinogenin (all glycosides reported so far were those of genuine aglycones only).

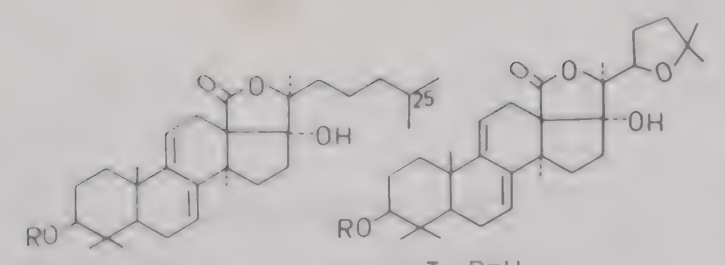
It is well known that the cuverian glands of sea cucumbers are particularly rich in *Holothuria* saponins. In the case of our collection of *H. atra*, we have found that the intenstines (containing cuverian tubules) possessed a larger concentration of these substances on weight basis and particularly on the basis of extractable organic matter. (On the basis of numbers, however, the amount was almost similar in the intestines and body walls.) In the case of *H. scabra*, the tubules could not be located and hence, the extraction of the whole animal was done.

*Examination of the intestines of H. atra*

From the acid hydrolysate (3*N* HCl, steam-bath, 3 hr) of the methanol extract, three aglycones A, B and C were isolated by column chromatography. Compounds A and B were identified as 22, 25-oxidoholothurinogenin (I)[3] and holothurinogenin (II)[5] based on spectral data† of I and II and those of the corresponding acetates Ia and IIa.

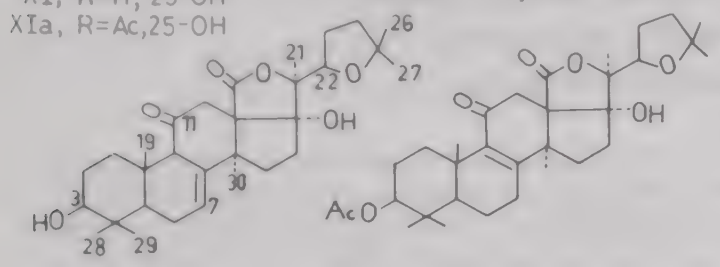
Compound-C, a new sapogenin, m.p. 280-82°, $M^+$ 500 (3%), $C_{30}H_{44}O_6$, also belonged to the class of *Holothuria* sapogenins. Its PMR spectrum is almost similar to that of I and the cyclic side-chain ethereal 22-H ($\delta$4.20, *t*, *J* = 7 Hz), 3-H (3.23, *m*) and a total of seven methyls could easily be recognised. However, the differences are that instead of two one-proton multiplets each in the olefinic region of I, there is only one neat triplet at the mid-point of these two in (C) ($\delta$5.37, *t*, *J* = 7 Hz), i.e., only one trisubstituted double bond is present. Also, the 19-Me and 30-Me in (C)

† PMR data of all the compounds isolated are given in Table 1.



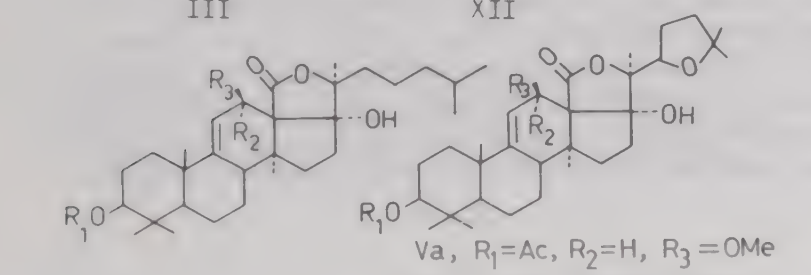
II, R=H; IIa, R=Ac
X, R=H, 25-OMe
Xa, R=Ac, 25-OMe
XI, R=H, 25-OH
XIa, R=Ac, 25-OH

I, R=H
Ia, R=Ac
VIII, R=xylose
VIIIa R=xylose triacetate



III

XII



IVa, $R_1$=Ac, $R_2$=H, $R_3$=OMe
VIa, $R_1$=Ac, $R_2$=OAc, $R_3$=H

Va, $R_1$=Ac, $R_2$=H, $R_3$=OMe
VIIa, $R_1$=Ac $R_2$=OAc $R_3$=H
IX, $R_1$=xyl-quin, $R_2$=OH, $R_3$=H
IXa, $R_1$=xyl-quin pentaacetate, $R_2$=OAc, $R_3$=H

appeared at positions which are deshielded and shielded respectively to the same extent ($\Delta = +0.14$ and $-0.13$ respectively) relative to those of I. In compound-C, the additional oxygen atom, in comparison to I, is ketonic in nature as revealed by the IR peak at 1700 $cm^{-1}$ in (C). The ketonic function in (C) could not be present in the side chain as it would mean a five-membered ring ketone. It could only be present in a six-membered ring proximate to the exocyclic trisubstituted double bond for the latter rearranged to the conjugated ($\Delta^8$) position (giving an $\alpha$, $\beta$-unsaturated ketone) even during $Py/Ac_2O$ acetylation. The rearranged product XII, m.p. 288-90 , $[\alpha]_D$ + 91.25°, $C_{30}H_{40}O_6$ is an acetate ($\nu_{max}$ 1735 $cm^{-1}$) containing an $\alpha$, $\beta$-unsaturated (disubstituted, $\lambda_{\mu\alpha x}$ 250 nm; $\varepsilon = 32{,}000$) six-membered ring ketone ($\nu_{max}$ 1680 $cm^{-1}$) i.e. the double bond is now tetracyclic. The same was also indicated in the PMR spectrum of XII showing absence of olefinic protons. Both the 19-Me and 30-Me of XII consequent on the shift of the double bond, underwent deshielding ($\Delta = +0.22$ and $+0.11$ respectively) relative to those of Ia.

From the above, even though other positions should also be considered for the keto function in (C), it could be present either at C-11 (giving $\Delta^7$-11-keto system) or at C-7 (giving $\Delta^{9(11)}$-7-keto system). The latter was ruled out by analogy with stichopogenin-$A_4$[6] and former supported by analogy with stichlorogenols[7].

Drieding models of the former having a 11-keto system have shown that the 19$\beta$-Me and 30$\alpha$-Me would fall similarly in its deshielding and shielding cones respectively, and hence, they would undergo equal lowfield or upfield shift relative to these groups in I. Thus, the structure of compound-C is elucidated as 11-keto-9(11)-dihydro-22, 25-oxidoholothurinogenin-$\Delta^7$-ene (III), further support being provided by its mass spectrum. *Holothuria* sapogenins with a $\Delta^7$ alone are quite rare[6,7] and with an additional keto function (usually at C-16) are further so[8]. A 11-keto system of III is the first report of its natural occurrence in *Holothuria* sapogenins.

*Examination of body walls of H. atra*

The acid hydrolysate under milder conditions (2*N* $H_2SO_4$, steam-bath, 1 hr) of the methanol extract was defatted with hexane and then fractionated using ethyl acetate and methanol. The former fraction on $SiO_2$ gel chromatography, gave mixtures I and II which were apparently homogeneous, but later separated by argentometric $SiO_2$ gel column chromatography of their acetates to compounds D, E and F, G respectively.

Compound D and B are both methyl ethers ($\delta$3.40, *s* and 3.41 *s* respectively for the 12$\beta$-OMe). The latter has been established as 3$\beta$-acetoxy-12$\beta$-methoxy-22, 25oxido-7, 8-dihydrorholothurinogenin (Va), the parent alcohol (V) being previously reported from *Actinopyga agassizi*[9]. Compound-D, m.p. 264-66°, $[\alpha]_D$-26°, $C_{33}H_{52}O_6$ resembles Va in UV, IR and PMR spectra, except that its side-chain is not cyclic (absence of 22-H in the PMR spectrum) but is a cyclic (secondary methyls at $\delta$0.88 *d*; $J = 7$ Hz) as in IVa. In the mass spectra, both IVa and Va did not show molecular ion peaks under electron impact but did show fragments at *m/z* 512 (23%) and 526 (66%) respectively arising by the loss of a molecule of MeOH from the molecular ion peaks. Compound-D is thus identified as the analogue of Va with an open side-chain, i.e., 3$\beta$-acetoxy-12$\beta$-methoxy-7, 8-dihydroholothurinogenin (IVa) which was previously isolated from the acid hydrolysate of the synthetic dihydroholothurin-A[9]. IVa is thus a new compound.

Compounds F and G correspond to D and E respectively except that the former are allylic acetates ($\delta$5.70 *m* and 5.80 *s* for the geminal protons) instead of allylic O-methyl ethers. The acetate groups in these allylic acetates, could only be present at C-12 giving them an $\alpha$ (axial)-configuration. The 30-methyl protons of F and G are at deshielded positions ($\delta$ 1.16 *s* and 1.14 *s* respectively) relative to those ($\delta$0.82 *s*) of a 12$\beta$ (equatorial) hydroxyaglycone[10] ($\Delta = -0.33$). A 1, 3-*cis* diaxial interaction is implicated for the large deshielding of 30-Me (with 12-OAc) in VI and VII.

Table 1—$^1$H NMR Spectra of Holothuria Compounds

| Compd | 3-H | 7-H | 11-H | 12-H | 22-H | 28&29 Me's | 19-Me | 30-Me | 21-Me | 26&27 Me's | Acetates | Others |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | 3.25 *m* | 5.5 *m* | 5.25 *m* | — | 4.20 *t*, *J*=7 Hz | 0.93 *s*<br>1.03 *s* | 1.12 *s* | 1.20 *s* | 1.36 *s* | 1.24 *s*<br>1.26 *s* | — | — |
| Ia | 4.48 *t* *J*=7 Hz | 5.45 *m* | 5.23 *m* | — | 4.15 *t* *J*=7 Hz | 0.89 *s*<br>0.94 *s* | 1.08 *s* | 1.16 *s* | 1.32 *s* | 1.19 *s*<br>1.22 *s* | 2.02 (3-OAc) | |
| II | 3.19 *m* | 5.46 *m* | 5.26 *m* | — | — | 0.82 *s*<br>0.98 *s* | 1.08 *s* | 1.13 *s* | 1.36 *s* | 0.93 *d* *J*=7 Hz<br>0.93 *d* *J*=7 Hz | — | — |
| IIa | 4.48 *t* *J*=7 Hz | 5.46 *m* | 5.24 *m* | — | — | 0.81 *s*<br>0.85 *s* | 1.11 *s* | 1.12 *s* | 1.37 *s* | 0.90 *d* *J*=7 Hz<br>0.90 *d* *J*=7 Hz | 2.02(3-OAc) | — |
| III | 3.23 *m* | 5.37 *t* *J*=7 Hz | — | — | 4.20 *t* *J*=7 Hz | 0.85 *s*<br>0.96 *s* | 1.26 *s* | 1.07*s* | 1.35 *s* | 1.26 *s*<br>1.26 *s* | — | 3.83 *br,s* (9-H) |
| IVa | 4.5 *m* | — | 5.35 *m* | 4.07 *m* | — | 0.87 *s*<br>0.91 *s* | 1.23 *s* | 1.04 *s* | 1.50 *s* | 0.88 *d* *J*=7 Hz<br>0.88 *d* *J*=7 Hz | 2.02(3-OAc)<br>3.40(12-OAc) | — |
| Va | 4.52 *m* | — | 5.32 *m* | 4.08 *m* | 4.08 *m* | 0.88 *s*<br>0.90 *s* | 1.26 *s* | 1.08 *s* | 1.40 *s* | 1.26 *s*<br>1.26 *s* | 2.05(3-OAc) | 3.41 (12-Me) |
| VIa | 4.50 *m* | — | 5.05 *m* | 5.70 *m* | — | 0.92 *s*<br>0.87 *s* | 1.24 *s* | 1.16 *s* | 1.32 *s* | 0.88 *d* *J*=7 Hz<br>0.88 *d* *J*=7 Hz | 2.07(12-OAc)<br>2.01(3-OAc) | — |
| VIIa | 4.48 *m* | — | 5.03 *s* | 5.80 *s* | 4.03 *t* *J*=7 Hz | 0.87 *s*<br>0.84 *s* | 1.22 *s* | 1.14 *s* | 1.33 *s* | 1.22 *s*<br>1.23 *s* | 2.04(12-OAc)<br>2.02(3-OAc) | 2.72 *m* 8−H |
| VIIIa | | 5.45 *m* | 5.20 *m* | — | 4.05-4.20 *m* | 0.85 *s*<br>0.93 *s* | 1.06 *s* | 1.14 *s* | 1.33 *s* | 1.20 *s*<br>1.22 *s* | 2.06 (3 acetate) | 4.8-5.05: protons geminal to OAc's<br>4.50 *d* *J*=7 Hz: $C_1'$-H<br>3.95-4.10 (4 *protons*)<br>4.30-4.70 (5 protons) |
| IXa | * | — | 5.05 *m* | 5.65 *m* | * | 0.84 *s*<br>0.97 *s* | 1.13 *s* | 1.18 *s* | 1.30 *s* | 1.20 *s*<br>1.20 *s* | 1.94(3-OAc)<br>1.98 (3 acetates)<br>2.03 (1 acetate)<br>2.06 (1 acetate) | |
| X | 3.23 *m* | 5.56 *m* | 5.21 *m* | — | — | 0.80 *s*<br>1.00 *s* | 1.08 *s* | 1.13 *s* | 1.40 *s* | 1.13 *s*<br>1.24 *s* | — | 3.15 *s* (25-OMe) |
| Xa | 4.53 *m* | 5.53 *m* | 5.28 *m* | — | — | 0.88 *s*<br>0.97 *s* | 1.15 *s* | 1.13 *s* | 1.40 *s* | 1.15 *s*<br>1.24 *s* | 2.03(3-OAc) | 3.17 *s* (25-OMe) |
| XIa | 4.50 *m* | 5.52 *m* | 5.30 *m* | — | — | 0.88 *s*<br>0.97 *s* | 1.13 *s* | 1.15 *s* | 1.43 *s* | 1.25 *s*<br>1.25 *s* | 2.07(3-OAc) | — |
| XII | 4.50 *m* | — | — | — | 4.20 *t* *J*=7 Hz | 0.92 *s*<br>0.92 *s* | 1.30 *s* | 1.27 *s* | 1.35 *s* | 1.22 *s*<br>1.25 *s* | 2.02(3-OAc) | — |

* Signal merged with others in the spectrum.

Thus, the two compounds were identified as 3$\beta$, 12$\alpha$-diacetoxy-7, 8-dihydroholothurinogenin (VIa)[11] and 3$\beta$, 12$\alpha$-diacetoxy-7, 8-dihydro-22, 25-oxidoholothurinogenin (VIIa)[12] respectively. Even though their corresponding diols, VI and VII were proposed as the genuine aglycones of Holothuria saponins, the saponins, themselves have not been so far isolated and their actual isolation now from the acid hydrolysate supports this proposal.

The methanol soluble portion of the acid hydrolysate was divided into two parts. One was subjected, to complete hydrolysis (3*N* HCl, steam-bath, 3 hr) when from the resulting hydrolysate, compounds A and B (vide supra) were isolated by $SiO_2$

gel chromatography. The second part was chromatographed directly (on $SiO_2$ gel) to give two glycosides H and K (positive Molisch test), the former containing only one sugar (xylose in equimolar proportion with the genin) and the latter, two (xylose and quinovose in 1:1:1 proportion with the aglycone). Glycoside-H contained a heteroannular diene moiety in its aglycone part ($\lambda_{max}$ 244 nm, $\varepsilon$ = 14,000) while glycoside K is devoid of this moiety i.e. the former is a glycoside of an artifact aglycone while the latter that of a genuine aglycone. However, both H and K yield the same genin on acid hydrolysis, which is identified as 22, 25-oxidoholothurinogenin (I). The PMR spectra of their peracetates, VIIIa and IXa ($Py/Ac_2O$, $\Delta$) resolved their structures a 3-O-(2′-β-D-quinovopyranosyl-β-D-xylypyranosyl) holothurigenol (IX) by comparison with literature data. Holothurin B of *Holothuria leucospilota* is a 4′-O-sodium sulfate of IX[12a].

*Examination of H. scabra*

The acid hydrolysate (complete, 3*N* HCl, steam-bath, 3 hr) of the methanol extract gave on $SiO_2$ gel chromatography, four compounds, two of which have been identified as I and II, the latter comprising a new report from *H. scapra*. The other two, namely, compounds L and M, based on their spectral data and those of their acetates, as 25-methoxy-holothurinogenin (X)[5] and its demethyl analogue, 25-hydroxyholothurinogenin (XI)[13] respectively. This is the first report of the occurrence of X and XII in *H. scabra*.

The chemical examination of the sea cucumber extracts has usually been fraught with complexities[9,10,14,15], for, during acid hydrolysis of the triterpenic glycosides, a genuine structural moiety of 12α-hydroxy-$\Delta^{9(11)}$ system is scarcely retained in the isolated aglycones. Or, a 12β-OH is produced (by epimerisation)[10] and so also methyl ethers at C-12 when very mild conditions (0.2 *N* HCl, 50°) are used[9,14]. In case of a 25-OH also, a 25-OMe might result[15]. All these possibilities as exemplified by the results of present study of *H. atra* and *H. scabra* arise due to the randomness of proton attack at different reactive centres. However, a point of interest and importance is that the cleavage of the quinovosexylose bond (cf IX) might be preceded by the conversion first of a 12α-hydroxy-$\Delta^{9(11)}$ system into the $\Delta^{7,9(11)}$-diene (cf VIII) because of a predominant 90% yield of the latter (from the glycoside mixture). Further, in both the species examined, the open side-chain is quantitatively less favoured for the sapogenins (or saponins) compared to the cyclic side-chain (integral ratio of open side-chain: cyclic side-chain, 1:3). Our studies have, moreover, not only provided the novel III as a genuine aglycone but also have shown that the other genuine aglycones VI and VIII can indeed be isolated, may be as minor components, surviving acid hydrolysis.

**Experimental Procedure**

Melting points were determined on VEB, Analytic Dreader HMK hot plate and are uncorrected. Column chromatography was done on silica gel (100-200 mesh, Acme) columns. All $R_f$ values refer to TLC using benzene-acetone mixture as an urgent unless otherwise specified. All pure compounds crystallised from methanol into colourless needles. They were dried for analysis at 60°/0.2 mm for 6 hr and were found to give satisfactory elemental analyses. The UV in EtOH and IR spectra in KPr matrix were recorded on Schimadzu-double beam and Schimadzu-408 spectrophotometers respectively. PMR spectra were run on a Perkin-Elmer R-32 instrument operating at 90 MHz in $CDCl_3$; chemical shifts in $\delta$-scale.

*Collection and processing of organisms*

*Holothuria atra* and *H. scabra* (150 numbers each) were collected during December, 1982 at neap tide when the organisms were exposed (the former in the upper and the latter in the lower reaches) at Mandapam Camp coast (N, 17°; E, 83°) in the south-eastern part of the Indian peninsula. They were washed thoroughly and processed immediately. They were dissected (when all the sea water within was removed) and the separated intestines and body walls (in the case of *H. ara*) were soaked in exzcess methanol before bringing them to the laboratory.

*Chemical examination of H. atra (intestines)*

The intestines (150 in number) were refluxed with methanol (5 litres) and the aqueous suspension (500 ml) obtained by evaporation of methanol was hydrolysed with HCl (3*N*, steam bath, 3 hr) and the gummy precipitate separated by decanting. It was dissolved in chloroform, dried ($Na_2SO_4$) and concentrated) to leave a gum (10 g) which was chromatographed (30 mm × 120 cm, 120 g gel) to collect the fractions (500 ml each) by gradient elution (see Table 2).

22, 25-*Oxidoholothurinogenin* (*I*):

Compound A, m.p. 301-02°, $R_f$ 0.42 (90:10), $[\alpha]_D$-21.2°, $C_{30}H_{42}O_5$; UV: 244 ($\varepsilon$ = 14,500), 237 (sh,

Table 2—Column Chromatography of Chloroform Solubles from Acid Hydrolysate of Methanol Extract of *H. atra* Intestines

| Fractions | Benzene-ethyl acetate | Compound present | Yield (mg) |
|---|---|---|---|
| 55-62 | 95:5 | A(I) | 500 |
| 63-70 | 90:10 | B(II) | 100 |
| 71-77 | 80:20 | C(III) | 300 |

13,500), 252 nm (sh: $\varepsilon$ = 10,500): (IR: 3500, 1750 $cm^{-1}$; MS: *m/z* 484 ($M^+$, 1%), 466 ($M^+ - H_2O$, 3), 397 ($M^+$-87, ring-A cleavage, 3), 99 (1, 1-dimethyl-tetrahydrofuran of side-chain, 100%). Compound A was identified by direct comparison with an authentic sample of (I) kindly provided by Prof I. Kitagawa, Osaka University, Japan.

Compound A acetate, Ia ($Py/Ac_2O$, room temp, 24 hr), m.p. 288-90°, $R_f$ 0.42 (80:20), $[\alpha]_D$ + 6.5°, $C_{32}H_{42}O_6$, UV: 245 nm ($\varepsilon$ = 15,000): IR: 3500, 1755, 1735, 1240, 1140 $cm^{-1}$.

*Holothurinogenin (II)*:

Compound B, m.p. 277.78°, $R_f$0.35 (90:10), $[\alpha]_D$ +94°, $C_{30}H_{40}O_4$; UV:245($\varepsilon$=17,000), 2135 (sh, $\varepsilon$ = 10,500), 250 nm (sh, $\varepsilon$ = 10,000); IR: 3500, 1750 $cm^{-1}$: MS: *m/z* 470 ($M^+$, 30%), 437 ($M^+ - H_2O - CH_3$, 21), 383 ($M^+$ − side chain, 42).

Compound B, acetate, IIa, m.p. 255-57°, $R_f$ 0.54 (80:20), $[\alpha]_D$ + 10°, $C_{32}H_{42}O_6$: UV: 244 nm ($\varepsilon$ = 17,500); IR: 3500, 1755, 1735 $cm^{-1}$.

*11-Keto-9-(11)-dihydro-22, 25-oxidoholothurinogenin (III)*

Compound C, m.p. 280-82°, $R_f$ 0.20 (90:10), $[\alpha]_D$ + 16.6°, $C_{30}H_{44}O_6$: no absorption in the UV above 220 nm; IR: 3500, 1740, 1700, 1140 $cm^{-1}$; MS: *m/z* 500 ($M^+$, 3%), 384 ($M^+$ − side chain + $H^+$, 26).

*3β-Acetoxy-11-keto-Δ⁸-7, 8, 9(11)-tetrahydro-22, 25-oxidoholothurinogenin (XII)*

This was obtained by acetylation ($Py/Ac_2O$, room temp, 24 hr) of III, m.p. 288-90°, $R_f$ 0.61 (80:20), $[\alpha]_D$ + 91.25°, $C_{32}H_{46}O_7$; UV: 250 nm ($\varepsilon$ = 32,000): IR 3500, 1770, 1735, 1680, 1380-1400, 1140 $cm^{-1}$.

*Chemical examination of H. atra (body walls)*

The methanol soaked body walls were cut into small pieces, shade-dried (48 hr) and extracted in a soxhlet with methanol (5 litres.). The methanol extract was concentrated to an aqueous suspension (1 litre) and hydrolysed with sulphuric acid (2*N*, steam bath, 1 hr). A grey precipitate was formed which was filtered, dried (18 g) and extracted with *n*-hexane, ethyl acetate and methanol. The residue from *n*-hexane, mainly containing waxes and oils was not pursued.

*Ethyl acetate extract*

The residue (4.5 g) from ethyl acetate extract, on chromatography (35 mm × 90 cm column, 160 g gel) gave by gradient elution with benzene-ethyl acetate (80:20) fractions (500 ml each) of 32-37 (mixture I, 120 mg) and 38-49 (mixture II, 100 mg). Mixtures I and II were initially mistaken as pure compounds with $R_f$ 0.53 and 0.30 (85:15), respectively. Their acetates, however, were each resolved into two spots of $R_f$ 0.72, 0.65 and 0.72, 0.67 (85:15) respectively, by silver nitrate (5%) impregnated silica gel (10 g) column (10 mm × 45 cm) chromatography (Table 3).

Table 3—Column Chromatography of Acetates of Mixtures I and II from Ethyl Acetate Solubles of Milder Acid Hydrolysate of Methanol Extract of *H. atra* (Body Walls)

| Fractions (100 ml each) | Compound present | Yield (mg) |
|---|---|---|
| | Mixture I | |
| 4-8 | D (IVa) | 30 |
| 9-11 | D+E | 10 |
| 12-20 | E (Va) | 70 |
| | Mixture II | |
| 7-12 | F (VIa) | 40 |
| 13-15 | F+G | 7 |
| 16-23 | F (VIIa) | 50 |

*3β-Acetoxy-12β-methoxy-7, 8-dihydro-holothurinogenin (IVa)*

Compound D, m.p. 264-68°, $R_f$ 0.72 (85:15), $[\alpha]_D$ −26° $C_{33}H_{52}O_6$; no absorption in the UV above 220 nm; IR 3500, 1750, 1735, 1380-1400, 1240 $cm^{-1}$; MS: *m/z* 544 ($M^+$, 0%), 512 ($M^+$ − MeOH 23), 452 ($M^+$ − MeOH − AcOH, 67).

*3β-Acetoxy-12β-methoxy-22, 25-oxido-7, 8-dihydroholothurinogenin (Va)*

Compound E, m.p. 284-85°, $R_f$ 0.65 (85:15), $[\alpha]_D$, −60°, $C_{33}H_{50}O_7$; no absorption in the UV above 220 nm; IR 3500, 1755, 1735, 1380-1400, 1240, 1135 $cm^{-1}$; MS: *m/z* 558 ($M^+$, 0%), 526 ($M^+$ − MeOH, 66), 466 ($M^+$ − MeOH − AcOH, 6), 99 (side chain, 100).

*3β, 12α-Diacetoxy-7, 8-dihydroholothurinogenin (VIa)*

Compound F, m.p. 248-50°. $R_f$ 0.72(85:15), $[\alpha]_D$ +70°, $C_{34}H_{52}O_7$; no absorption in the UV above 220 nm; IR: 3500, 1755, 1735, 1735, 1380-1400, 1240 $cm^{-1}$; MS: *m/z* 572($M^+$, 0%), 513($M^+ - CO_2 - Me$, 38), 512 ($M^+$ − AcOH, 100), 453 ($M^+ - CO_2$ − AcOH, 58), 393 ($M^+ - CO_2$ − Me − 2AcOH, 75).

*3β, 12α-Diacetoxy-7, 8-dihydro-22,25-oxidoholothurinogenins (VIIa)*

Compound G, m.p. 258-60°, $R_f$ 0.67 (85:15), $[\alpha]_D$ +173.17°, $C_{34}H_{50}O_8$; no absorption in the UV above 220 nm; IR: 3500, 1755, 1735, 1380-1400, 1240, 1135 $cm^{-1}$; MS: *m/z* 586 ($M^+$, 0%), 542 ($M^+ - CO_2$, 2), 526 ($M^+$ − AcOH, 42), 451 ($M^+$ − 2AcOH − Me, 2), 99 (side chain, 100).

*Reaction of compounds D, E, F and G with HCl*

Each compound (10 mg) in dioxane (2 ml) and HCl (3*N*, 1 ml) was heated on a steam bath (3 hr). Usual work-up, gave holothurinogenin (II) from D and F and 22, 25-oxodoholothurinogenin (I) from E and G.

*Methanol extract*

The residue (1.6 g) from methanol extract was divided into two parts. One part (400 mg) in methanol (100 ml) was refluxed (3 hr) with HCl (3*N*, 20 ml). The grey precipitate formed was extracted into chloroform after evaporation of methanol and the residue (300 mg) therefrom was chromatographed (10 mm × 45 cm column, 10 g gel). Gradient elution while using benzene-ethyl acetate (85:15) gave from fractions (50 ml each) 9-14 22, 25-oxidoholothurinogenin (I, 160 mg) and from fractions 19-26 holothurinogenin (II, 60 mg).

The second part of methanol extract (1.2 g) was chromatographed directly (45 mm × 100 cm column. 150 g gel). During gradient elution with chloroform-methanol (95:5), the fractions (250 ml each) 21-26 gave glycoside H (400 mg) and fractions 33-34 gave glycoside K (25 mg). The intermediate fractions 27-32 gave a mixture of H and K.

*3-O-(β-D-Xylopyranosyl)22, 25-oxidoholothurinogenin (VIII)*

Glycoside H, m.p. 263-65°, $R_f$ 0.50 (chloroform-methanol, 90:10), $C_{35}H_{52}O_9$; UV:244 nm ($\varepsilon = 14,000$); IR: 3400, 1750, 1380-1400, 1050 $cm^{-1}$.

Glycoside H peracetate (VIIIa), m.p. 301-2°, $R_f$0.68 (chloroform-methanol, 90:10), $[\alpha]_D - 31.25°$. $C_{41}H_{58}O_{12}$; UV:244 nm ($\varepsilon = 14,000$); IR: 3500, 1755, 1735, 1240 $cm^{-1}$.

*3-O-(2'-β-D-Quinovopyranosyl-β-D-xylopyranosyl-)holothurigenol (IX)*

Glycoside K, m.p. 280-82°, $R_f$ 0.52 (chloroform-methanol, 80:20), $[\alpha]_D$-10.2°, $C_{41}H_{64}O_{14}$: no absorption in the UV above 220 nm; IR: 3400-3500, 1755, 1625, 1350-1380, 1050 $cm^{-1}$.

Glycoside K peracetate (IXa), m.p. 255-57°, $R_f$ 0.53 (chloroformmethanol, 95:5), $[\alpha]_D$ + 10°, $C_{53}H_{76}O_{20}$, no absorption in the UV above 220 nm, IR: 3500, 1770, 1735, 1140 $cm^{-1}$.

*Acid hydrolysis of glycosides H and K*

In separate experiments, glycosides H and K (5 mg) in methanol (10 ml) and HCl (3*N*, 5 ml) were refluxed (3 hr) and the aglycone in each case identified as 22, 25-oxidoholothurinogenin (I). The sugar residue in the case of glycoside H was identified as xylose (Direct comparison) and those from glucoside K as xylose and quinovose.

Table 4—Column Chromatography of Chloroform Solubles of Acid Hydrolysate from Methanol Extract of *H. scabra*

| Fractions | Eluant (Benzene-ethyl acetate) | Compounds present | Yield (mg) |
|---|---|---|---|
| 48-55 | 95:5 | I | 300 |
| 56-63 | 90:10 | II | 40 |
| 64-70 | 85:15 | Compound L (X) | 40 |
| 79-85 | 75:25 | Compound M (XI) | 40 |

*Chemical examination of H. scabra*

The animals (150 in number) which were dissected and soaked in methanol in the field, were dried under shade (48 hr). The dried material (1 kg) was extracted in a soxhlet with hot methanol (5 litres), concentrated the aqueous residue (500 ml) obtained by evaporation of methanol was hydrolysed (steam bath, 3 hr) with HCl (3*N*, 150 ml). The grey precipitate formed was extracted into chloroform (5 × 200 ml), the chloroform extract dried, concentrated and the residue (11 g) chromatographed (30 mm × 60 cm column, 180 g gel). Gradient elution gave the fractions (500 ml each) as in Table 4.

*25-Methoxyholothurinogenin (X)*

Compound Lm.p. 288-90°, $R_f$.30 (80:20), $[\alpha]_D$ +%/°, $C_{31}H_{48}O_5$; UV: 247 nm ($\varepsilon = 19,000$); IR: 3500, 1755 $cm^{-1}$.

Compound L acetate (Xa), m.p. 277-79°, $R_f$ 0.48 (90:10), $[\alpha]_D$ + 8.6°, $C_{33}H_{50}O_6$; UV: 245 nm ($\varepsilon = 18,000$); IR: 3500, 1755, 1735 $cm^{-1}$.

*25-Hydroxyholothurinogenin (XI)*

Compound M, m.p. 298-300°, $R_f$ 0.56 (70:30), $[\alpha]_D$ + 48°, $C_{30}H_{46}O_5$; UV: 246 nm ($\varepsilon$ = 14,500); IR: 3500-3550, 1750 $cm^{-1}$. .

Compound M acetate (XIa), m.p. 287-88°, $R_f$ 0.57 (90:10), $[\alpha]_D$ 0.87°, $C_{32}H_{48}O_6$; UV: 244 nm ($\varepsilon = 17,500$); IR: 3500, 1755, 1735 $cm^{-1}$.

**Acknowledgement**

The authors thank the UGC, New Delhi for financial assistance and Dr D B James, CMFRI, Madras for identification of the sea cucumbers.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 722-724

# 21-Hydroxylanosterol, a New Lanostane Derivative from Stem Bark of *Uvariastrum zenkeri* Engl. & Diels

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*Received* 6 *August* 1986; *revised and accepted* 7 *January* 1987

21-Hydroxylanosterol [**3**; lanosta-8(9), 24(25) diene-3β,21-diol, a new lanostane derivative, has been isolated from the stem bark of *Uvariastrum zenkeri* Engl. and Diels (fam. Annonaceae) and characterized on the basis of spectral data, notably high-field PMR and $^{13}C$ NMR data. Biogenetically, it has been considered that 3, uvariastrol (**1**) and polycarpol (**2**), the last two also isolated from *U. zenkeri* [*Phytochemistry*, **23** (1984) 2077], are derived from a common cycloartane precursor.

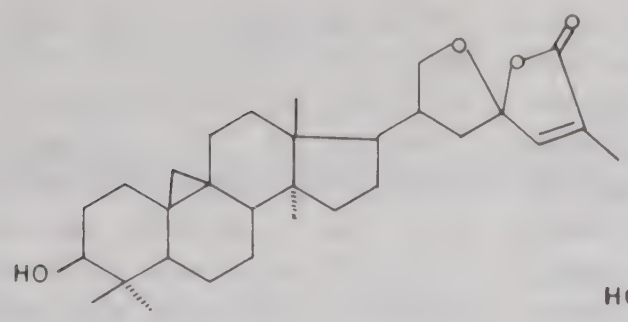
*Uvariastrum zenkeri*, a rain forest tree, is widely found in southeast Nigeria and Cameroun[1]. An earlier[2] phytochemical investigation has revealed the occurrence of uvariastrol (**1**), a cycloartane triterpene, and a large amount of polycarpol (**2**)[2,3] in the stem bark of this plant. Further chemical investigation of the stem bark of this tree has now yielded a novel lanostane triterpene derivative, 21-hydroxylanosterol (**3**) which has been provisionally named as uvariol. Structure elucidation of **3** forms the subject matter of this paper.

21-Hydroxylanosterol (**3**) was obtained as a colourless solid in 0.001% yield from the pet. ether extract of the stem bark using CPTLC over silica gel P-254. The accurate mass measurement of **3** gave the molecular ion corresponding to the elemental composition $C_{30}H_{50}O_2$. This suggested the natural product to be a triterpene which showed IR bands for hydroxy group(s) (3300-3500 $cm^{-1}$). The PMR spectrum exhibited five singlets at δ 0.98, 0.96, 0.88, 0.79 and 0.68 attributable to the tertiary methyls occupying positions 19, 30, 28, 29 and 18 respectively of a lanostane triterpene[4,5]. This was supported by the $^{13}C$ NMR spectrum which displayed signals in close agreement with those published for ring carbons and attached methyls of lanostenol[6] (**4**; Table 1). Appearance of a double doublet at δ 3.21 ($J$=11.4 and 4.3 Hz) was indicative of an axial oxymethine proton, suggesting the usual equatorial (β) orientation for the hydroxy group at C-3. This was supported by the $^{13}C$ NMR signal at δ 78.9 (*d*) which agreed closely with that recorded for the C-3 carbon with β-hydroxy group in polycarpol and lanostenol[6]. In view of the close similarities between the $^{13}C$ NMR spectra of **3** and lanostenol (**4**), the remaining single oxygen must be placed at C-17 side chain. This was confirmed by

Table 1—$^{13}C$ NMR Chemical Shifts of 21-Hydroxylanosterol (**3**), Lanostenol (**4**), Polycarpol (**2**) and Ophioboline-D (**5**)

| Carbon No. | **3** | Lanostenol[6] (**4**) | Polycarpol[7] (**2**) | **5**[9] |
|---|---|---|---|---|
| 1 | 35.6 (*t*) | 35.8 | | |
| 2 | 27.9 (*t*) | 27.9 | | |
| 3 | 78.9 (*d*) | 79.0 | | |
| 4 | 38.8 (*s*) | 39.0 | | |
| 5 | 49.0 (*d*) | 50.5 | | |
| 6 | 19.1 (*t*) | 19.2 | | |
| 7 | 28.1 (*t*) | 28.3 | | |
| 8 | 134.3 (*s*)* | 134.4 | | |
| 9 | 134.4 (*s*)* | 134.4 | | |
| 10 | 37.1 (*s*) | 37.2 | | |
| 11 | 20.9 (*t*) | 21.1 | | |
| 12 | 26.4 (*t*) | 26.7 | | |
| 13 | 44.2 (*s*) | 44.6 | | |
| 14 | 49.8 (*s*) | 49.9 | | |
| 15 | 31.3 (*t*) | 31.2 | | |
| 16 | 30.7 (*t*) | 31.0 | | |
| 17 | 50.3 (*d*) | 50.7 | | |
| 18 | 15.9 (*q*) | 15.9 | | |
| 19 | 18.2 (*q*) | 18.3 | | |
| 20 | 35.5 (*d*) | 36.5 | 35.7 | 32.4 |
| 21 | 62.6 (*t*) | — | — | — |
| 22 | 37.3 (*t*) | 36.5 | 38.5 | 37.7 |
| 23 | 26.1 (*t*) | 24.2 | 24.8 | 26.1 |
| 24 | 124.8 (*d*) | — | 124.8 | 124.8 |
| 25 | 131.3 (*s*) | — | 131.3 | 130.7 |
| 26 | 17.6 (*q*) | — | 17.0 | 17.5 |
| 27 | 25.6 (*q*) | — | 25.7 | 25.6 |
| 28 | 24.3 (*q*) | 24.3 | — | — |
| 29 | 15.3 (*q*) | 15.4 | — | — |
| 30 | 28.0 (*q*) | 28.1 | — | — |

EIMS of **3** (Chart 1) which exhibited a fragment ion at *m/z* 127 [**6**; $(C_8H_{15}O)^+$] representing the entire C-17 side chain. This ion lost a molecule of water to give the ion at *m/z* 109 $(C_8H_{13})^+$ suggest-

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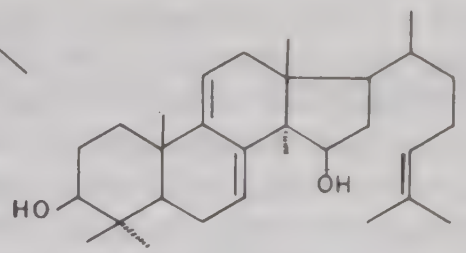


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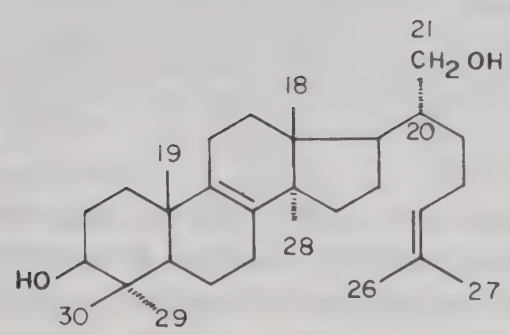


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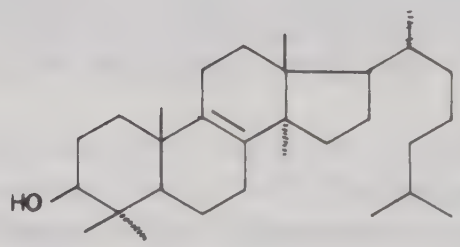


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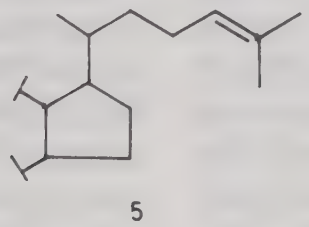

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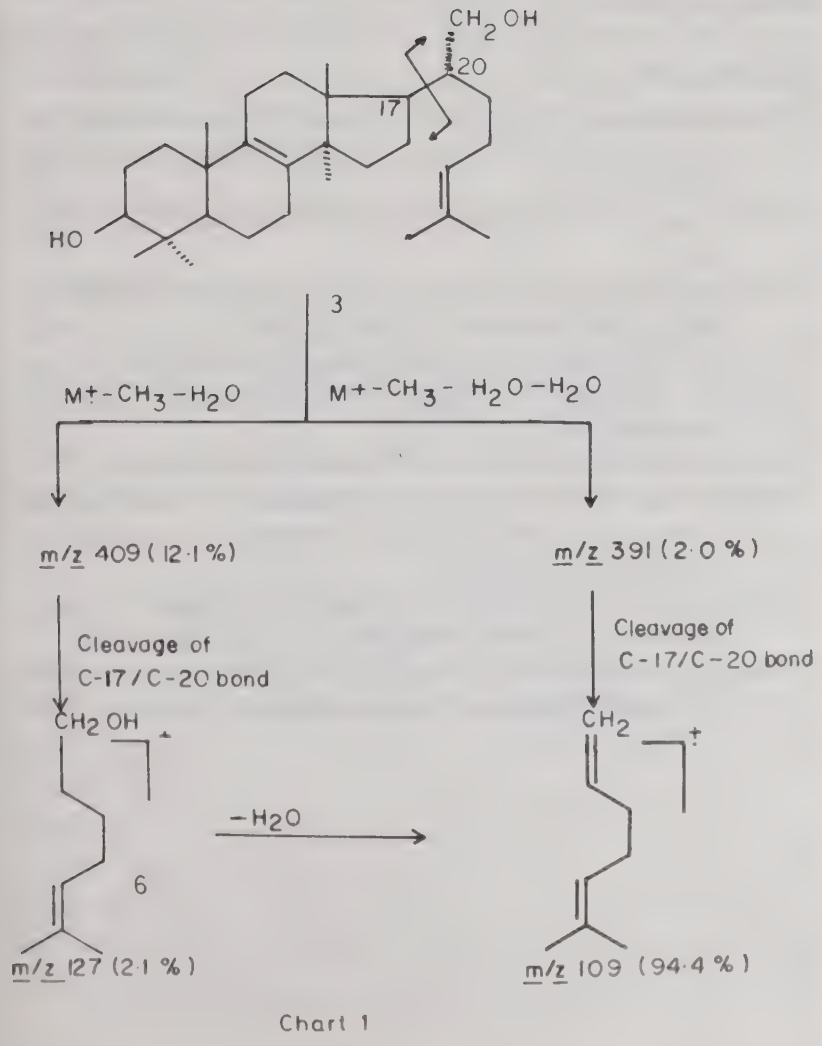


Chart 1

ing the presence of an OH group in the side chain. The PMR spectrum of **3** displayed signals corresponding to the *AB* part of an *ABX* system at δ 3.61 and 3.71 (each *dd*, $J = 11.2$, 4.6 and 11.4, 4.3 Hz respectively), suggesting the presence of a $-\underset{|}{CH}-CH_2-OH$ moiety. This was confirmed by the appearance of a triplet at δ 62.6 in the $^{13}C$ NMR spectrum which was typical of $R-CH_2-OH$[8]. The presence of a lanostenol type side chain in **3** was evident from the close similarities in the carbon resonances (except at C-21) of **3** with those published for this type of side chain in polycarpol and ophioboline-D (**5**)[9]. The PMR spectrum was also consistent with this type of side chain, which showed two vinylic methyls at δ 1.56 and 1.66 and an olefinic proton at 5.10 ($t$, $J = 7.2$ Hz, H-24). The location of a primary hydroxy at C-20 was confirmed by the absence of a typical C-21 methyl doublet around δ 0.90 in the 360 MHz PMR spectrum.

Based on the above observations the structure of uvariol was established as 21-hydroxylanosterol [**3**; lanosta-8(9),24(25)diene-3β,21-diol], a compound not previously reported from a natural source.

However, its coexistence with uvariastrol (**1**), a novel cycloartane triterpene isolated from the same material, suggested a clear cut biogenetic relationship between these two compounds. The bicyclic tetrahydrofuran/furanone side chain of **1** could undergo ring opening and decarboxylation which could yield the corresponding cycloartane with a side chain system of **3**. However, given the relative ease with which cycloartane undergoes rearrangement to give the unsaturated 10-methyl-9(11)-ene derivatives, it must be considered likely that 21-hydroxy-8(9)-ene-lanostenol (**3**) and 7(8),9(11)-diene-polycarpol (**2**; reported from several Annonaceae species[3] and also present in *U. zenkeri*) are derived biogenetically from the same cycloartane precursor.

## Experimental Procedure

Melting point was determined on a Köfler Hot plate apparatus and is uncorrected. IR spectrum was recorded in KCl on a Perkin-Elmer 157 spectrophotometer. PMR and $^{13}C$ NMR spectra were run in $CDCl_3$ on a Brucker WH 360 (360 and 90.56 MHz) instrument using TMS as internal standard. Electron-impact mass spectrum (EIMS) was run on an AEI MS 902 spectrophotometer at 70 eV using a probe temperature 120-150°. Pet. ether specifically refers to the fraction having b.p. 40-60°.

The stem-bark of *Uvariastrum zenkeri* Engl. and Diels. (fam. Annonaceae) was collected from the Korup National Park, Cameroun. A voucher specimen (D.W. Thomas 604) was deposited at the Herbarium of the Royal Botanic Gardens, Kew, UK.

*Isolation of the triterpene*

The sun dried stem-bark (150 g) was powdered and extracted continuously in a soxhlet apparatus for three days with pet. ether. Preliminary column chromatography of the concentrated extract gave a mixture of triterpenes which was subsequently resolved on a chromatotron [CPTLC, chromatotron model No. Merck 7924, 1 mm silica gel disc, solvent: Toluene-EtOAc-AcOH (80:6:0.1)] to give **3** (15 mg) which crystallized from EtOAc as a colourless solid, m.p. 145-47°; $R_f$ 0.35 in toluene-EtOAc-AcOH (80:18:2) (Found: $M^+$ 442.3814. $C_{30}H_{50}O_2$ requires $M^{+\cdot}$ 442.3811); IR: 3300-3500 (OH), 2930 and 1000 $cm^{-1}$; PMR: δ 5.10 (1H, *t*, $J$=7.2 Hz, H-24), 3.71 (1H, *dd*, $J$=11.4 and 4.3 Hz, H-21), 3.61 (1H, *dd*, $J$=11.2 and 4.6 Hz, H-21), 3.21 (1H, *dd*, $J$=11.4 and 4.3 Hz, H-3α), 1.66 and 1.59 (2×3H, 2×*s*, 26 and 27-Me), 0.98 (3H, *s*, 19-Me), 0.96 (3H, *s*, 30-Me), 0.88 (3H, *s*, 28-Me), 0.79 (3H, *s*, 29-Me), and 0.68 (3H, *s*, 18-Me); $^{13}C$ NMR (see Table 1); EIMS (rel. intensity): *m/z* 442 ($M^{+\cdot}$; 23.7%), 427 ($M^{+\cdot}-Me$; 15.1%), 409 ($M^{+\cdot}-Me-H_2O$; 12.1%), 391 ($M^{+\cdot}-Me-H_2O-H_2O$; 2.0%), 315 [$(C_{22}H_{35}O)^+$; 1.4%], 313 [$(C_{22}H_{33}O)^+$; 19.4%], 311 [$(C_{22}H_{31}O)^+$; 16.7%], 281 [$(C_{22}H_{24})^+$; 3.0%], 271 [$(C_{19}H_{27}O)^+$; 29.4%], 253 [$(C_{19}H_{25})^+$; 15.6%], 227 [$(C_{17}H_{23})^+$; 14.8%], 213 [$(C_{18}H_{21})^+$; 10.0%], 185 [$(C_{11}H_{21}O_2)^+$; 18.7%], 135 [$(C_{10}H_{15})^+$; 44.6%], 127 [$(C_8H_{15}O)^+$; 2.1%], 119 [$(C_9H_{11})^+$; 56.4%], 110 [$(C_8H_{14})^+$; 20.9%] and 109 [$(C_8H_{13})^+$ (*m/z* 127 $-H_2O$); 100%]. Due to paucity of the compound (**3**), neither its optical rotation could be recorded nor its acetate derivative could be prepared.

## Acknowledgement

The authors wish to thank Dr P G Waterman, Department of Pharmacy, University of Strathclyde, UK for the supply of plant material and high field PMR, $^{13}C$ NMR and mass spectra. One of the authors (IM) is thankful to ACU for the award of a scholarship, under which this work has been carried out at the Phytochemistry Research Lab. (Department of Pharmacy), University of Strathclyde, Glasgow, UK.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 725-727

# Addition of Phthalimidonitrene to Substituted N-Benzenesulphonylindoles

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*Received* 17 *December* 1986; *accepted* 11 *February* 1987

The aziridines (**2a, b**) obtained by the addition of phthalimidonitrene to N-benzenesulphonylindole and N-benzenesulphonyl-2-phenylindole, respectively give the substituted quinazolines (**3a, b**) and the parent indole, when treated with methanolic KOH. However, the nitrene adduct **2c** derived from N-benzenesulphonyl-1-oxo-1,2,3,4-tetrahydrocarbazole under similar condition gives 1-hydroxycarbazole and 1-oxo-1,2,3,4-tetrahydrocarbazole (**4c**). Hydrazinolysis of the aziridines (**2a, b, c**) gives N-sulphonatedindoles through the N-amidoaziridine intermediate.

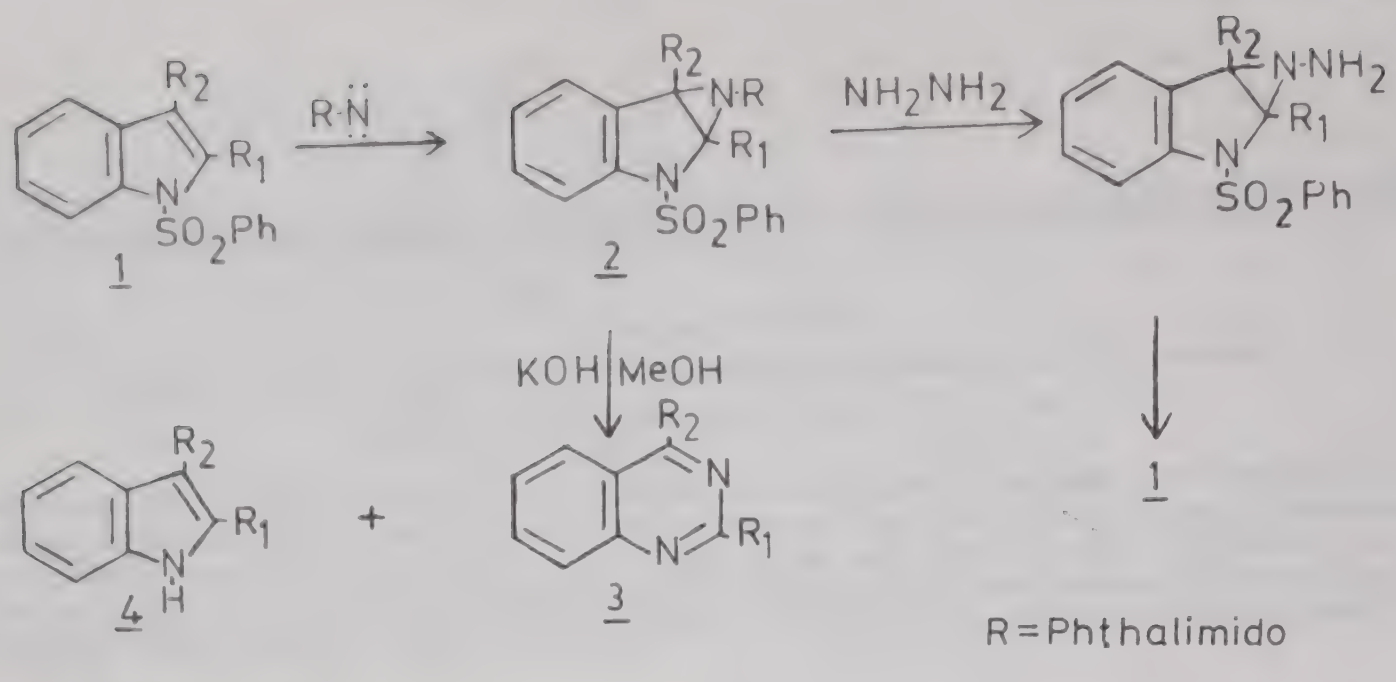
Phthalimidonitrene generated by the oxidation of N-aminophthalimide with lead tetraacetate undergoes facile addition to a variety of olefins[1] to form cyclic adducts, which have been used as potential synthons for the construction of azepine[2] and pyridine rings[3]. The present report explores the utility of phthalimidonitrene towards the synthesis of quinazoline derivatives. Bailey carried out the reaction of sulphonyl azides with indole[4,5] and substituted indoles[6] in the hope of getting aziridines; instead the reaction resulted in the formation of 2-sulphonamidoindoles.

Addition of oxidatively generated phthalimidonitrene to indole has been unsuccessful as indole itself is known to be sensitive towards oxidising agents. Hence nitrene transfer reaction has been attempted on indole. Jones[7] has reported thermal generation of phthalimidonitrene by the cycloreversion of the nitrene adduct derived from 2-acetylbenzofuran. Such attempts on indole did not yield the nitrene adduct.

N-Benzenesulphonylindole is stable towards lead tetraacetate and therefore the nitrene adduct (**2a**) derived from it and phthalimidonitrene could be used as synthon for quinazoline synthesis. The yellow crystalline adduct **2a** in its IR spectrum exhibits carbonyl and sulphonyl absorptions at 1750, 1720, 1180 and 1120 $cm^{-1}$. The PMR spectrum of **2a** exhibits the aziridine protons as one-proton doublet each at δ 2.178 and 2.046. As one of the aziridine protons is flanked by two nitrogen atoms, it is relatively shielded and hence appears high field. The disappearance of $C_3$-H signal of indole at δ 6.1 rules out the possibility of a 2-sulphonamideindole structure which is formed in the reaction of arylsulphonyl azide with indole. In addition, the IR and PMR spectra do not show the presence of N-H moiety, thus providing evidence in support of the proposed structure. Further evidence for **2a** is provided by the appearance of molecular ion peak at *m/z* 417 in its mass spectrum. The difference in the mode of reactivity of sulphonylnitrene and phthalimidonitrene could be due to the nucleophilicity associated in the latter. When treated with methanolic KOH **2a** affords quinazoline (**3**) and indole (**4**). The yield of quinazoline is suppressed because of the preferential attack of KOH on the carbonyl function.

The synthetic utility of the above route has been further explored with N-benzenesulphonyl-2-phenylindole. The red crystalline cycloadduct **2b** derived from phthalimidonitrene and N-benzenesulphonyl-2-phenylindole, when treated with methanolic KOH afforded 2-phenylquinazoline (**3b**) and 2-phenylindole (**4b**). Extension of the above synthetic procedure on the nitrene adduct derived from N-benzenesulphonyl-1-oxo-1,2,3,4-tetrahydrocarbazole was expected to give rise to a bicyclic system. Reaction of 1-oxo-1,2,3,4-tetrahydrocarbazole (**4c**) with benzenesulphonyl chloride in the presence of dimsyl anion gave the N-benzenesulphonyl derivative which underwent cycloaddition with phthalimidonitrene to give the adduct **2c**. The adduct **2c** when treated with methanolic KOH gave 1-hydroxycarbazole and the desulphonated carbazole. The formation of 1-hydroxycarbazole can be explained by a sequential elimination and enolisation process.

The aziridine (**2b**) when treated with hydrazine hydrate in ethanol at 50° gave a viscous oil which on purification afforded N-benzenesulphonyl-2-phenylindole (95%). The formation of N-benzenesulphonyl-2-phenylindole could result either by a thermal cycloreversion route or through an intermediacy of unstable N-aminoaziridine. Since the aziridine (**2b**) has been found to be thermally stable, the intermediacy of N-aminoaziridine was investigated. The aziridine (**2b**) on treatment with hydrazine hydrate afforded a dark coloured product, which in its IR spectrum displayed the presence of $\nu NH_2$ mode at




a, $R_1 = R_2 = H$

b, $R_1 = Ph; R_2 = H$

c, $R_1$ & $R_2$ = -C-$(CH_2)_3$-

3380 and 3340 $cm^{-1}$ and the absence of phthalimidocarbonyls. The N-aminoaziridine on heating underwent cycloreversion to give the parent indole. Similarly, the aziridines (**2a**) and **(2c)** gave N-benzenesulphonylindole and N-benzenesulphonyl-1-oxo-1,2,3,4-tetrahydrocarbazole respectively.

**Experimental Procedure**

Melting points are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 598 spectrometer and PMR spectra on a Varian EM 390 (90 MHz) instrument, chemical shifts are reported in δ-scale (ppm) downfield from TMS internal reference. Mass spectra were obtained at 70 eV. C, H and N analytical values for the nitrene adducts are found to be within the limits of error. In general, the work-up procedure involved washing the organic phase with water, drying over $MgSO_4$, and removing the solvent under reduced pressure. The residue obtained was recrystallised from an appropriate solvent.

*Addition of phthalimidonitrene to N-benzenesulphonylindoles*

To a stirred solution of N-aminophthalimide (0.011 mol) and N-benzenesulphonylindole (0.01 mol) in dichloromethane (30 ml) at 0°C was added lead tetraacetate (0.012 mol) slowly. Usual work-up and recrystallisation from petrol-ethyl acetate afforded **2a**.

Similar addition of phthalimidonitrene to **1b** and **1c** (3.33 g/3.25 g) gave the aziridines **2b** and **2c** (4.44 g, 95%, 3.64 g, 85%).

**2a**: m.p. 167-68°; IR 3100, 1750, 1720, 1600, 1400, 1180, 1120, 1100, 1080 $cm^{-1}$; PMR 7.90-7.65 and 7.55-7.21 (*m*, 13H), 2.178 (*d*, 1H, 3Hz), 2.046 (*d*, 1H, 3Hz); MS: *m/z* 417 ($M^+$).

**2b**: m.p. 238°; IR 3200, 3050, 1740, 1720, 1600, 1470, 1390, 1360, 1310, 1270, 1240, 1180, 1120, 1100, 1060 $cm^{-1}$; PMR 7.89-7.71 and 7.61-7.22 (*m*, 18H), 2.22 (**s**, 1H); MS: *m/z* 493 ($M^+$).

**2c**; m.p. 155°; IR 2975, 1775, 1740, 1660, 1470, 1180, 1140, 1080, 1060 $cm^{-1}$; PMR 7.82-7.71 and 7.50-7.21 (*m*, 13H), 2.75 (*t*, 2H, 7Hz), 2.51 (*t*, 2H, 7Hz), 2.20 (*q*, 2H, 7Hz); MS: *m/z* 485 ($M^+$).

*Reaction of the aziridines* (**2a, b, c**) *with methanolic KOH*

A solution of the N-benzenesulphonylaziridine (0.001 mol) in 10% methanolic KOH (20 ml) was stirred for 1 hr. Methanol was evaporated and the residue was extracted with ethyl acetate and worked-up as usual.

Aziridines **2a, b, c** (0.417 g, 0.493 g, 0.485 g) with methanolic KOH gave indole (0.09 g/80%), quinazoline (0.03 g, 20%), 2-phenylindole (0.136 g, 70%), 2-phenylquinazoline (0.06 g, 30%) and 1-hydroxycarbazole (0.06 g, 20%); 1-oxo-1,2,3,4-tetrahydrocarbazole (0.10 g, 80%) respectively.

*Hydrazinolysis of aziridines* (**2a, b, c**)

To a stirred suspension of the aziridine (0.001 mol) in ethanol (20 ml) a 98% solution of hydrazine (0.004 mol) in ethanol (10 ml) was added at 50° dur-

ing 10 min. The reaction mixture after stirring for 1 hr was poured onto ice and worked-up as usual.

Hydrazinolysis of **2a, b, c** (0.417 g/0.493 g/0.485 g) afforded **1a, b, c** (0.23 g, 95%/0.22 g, 65%/0.22 g, 68%) respectively.

*Low temperature hydrazinolysis of the aziridine* (**2b**)

To a solution of **2b** (0.493 g) in ethanol (10 ml) at −10°C, a solution of hydrazine hydrate (0.5 ml) in ethanol (2 ml) was added and stirred for 5 min. The reaction mixture was extracted immediately with dichloromethane, washed with ice water to remove hydrazine hydrate and dried ($K_2CO_3$) for a short period. A dark coloured solid was obtained after removing the solvent at low temperature (−10°C), m.p. 135°; IR ($CHCl_3$) 3380, 3340, 3020, 1610, 1520, 1180, 1160, 1120 $cm^{-1}$.

**Acknowledgement**

The author is grateful to Prof K Rajagopalan and Prof P C Srinivasan for encouragement; to Dr R. Balasubramanian, for the IR and PMR spectral data and to Dr T Perumal Pillai, University of Illinois for mass spectra and analytical data.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 728-730

# Michael Additions on *o*-Hydroxystyrylisoxazoles & Cyclireduction of Adducts

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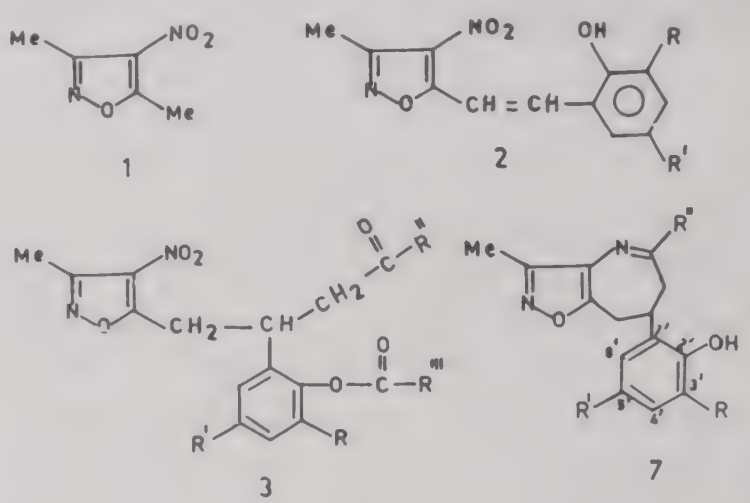
*Received* 4 *December* 1986; *accepted* 10 *February* 1987

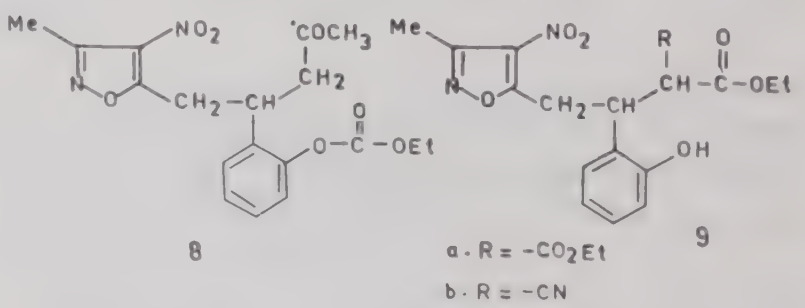
The interaction of Michael donors benzoylacetone, ethyl acetoacetate, ethyl cyanoacetate and diethyl malonate with 3-methyl-4-nitro-5-(*o*-hydroxystyryl)isoxazoles (**2**) leads to the Michael adducts (**3, 8, 9a** and **9b**). The formation of **3** and **8** is attended by an intramolecular transfer of functionalities. The cyclireduction of **3** and **8** to isoxazolo[7,8-*b*]azepines (**7**) has been used as a proof in support of intramolecular migration.

In a programme directed towards the synthesis of isoxazolo[7,8-*b*]azepines in two steps, viz. Michael addition and reductive cyclisation of the intermediates, we employed isoxazoles as Michael donors[1] as well as acceptors[2]. It was shown that when the donor was acetylacetone and the acceptor 5-*o*-hydroxystyrylisoxazole (**2**), the formation of adduct was attended by an intramolecular C → O acetyl migration. In the present investigation we have studied the interaction of a variety of Michael donors, mostly β-dicarbonyl compounds with **2** to have a deeper insight into the nature of the intramolecular migration during Michael addition. Conversion of the adducts into isoxazoloazepines is also reported.

3-Methyl-4-nitro-5-(*o*-hydroxystyryl)isoxazoles (**2**) were prepared by regiospecific styrylation of 3,5-dimethyl-4-nitroisoxazole (**1**) under Knoevenagel conditions in boiling ethanol. In the Michael reaction between **2** and benzoylacetone carried out in refluxing triethylamine, the products formed have been characterised as 4-(*o*-acetoxyphenyl)-5-(3-methyl-4-nitro-5-isoxazolyl)-2-pentanones (**3a-e**) on the basis of chemical and spectral data. The 2-pentanone (**3**) was obtained as a result of intramolecular acetyl group transfer from carbon to oxygen. The adducts (**3**) were neither soluble in dil. sodium hydroxide nor gave positive ferric reaction indicating the absence of enolic or phenolic group present in the starting compounds.

The formation of adducts (**3a-e**) can be rationalised as shown in Scheme 1. The first step is the usual Michael addition of the active methylene compound to the styrylisoxazoles. The enolic form of the Michael adduct (**4**) undergoes an internal addition to intravinyl moiety leading to the unstable spiro compounds (**5**) which is set for the acetyl transfer. After the acetyl migration the latter (**6**) is opened by the base resulting in the 2-pentanones (**3**).




The cyclireduction of the Michael adducts (**3a-e**) has been carried out on a steam-bath with stannous chloride and conc. hydrochloric acid. Chemical and spectral data show that the products of the reduction are 3-methyl-5-phenyl-7-*o*-hydroxyaryl-7,8-dihydro-6*H*-isoxazolo[7,8-*b*]azepines (**7a-c**) (Table 1). The presence of ηOH at 3100 $cm^{-1}$ and the absence of carbonyl group in the IR spectra of **7** sup-

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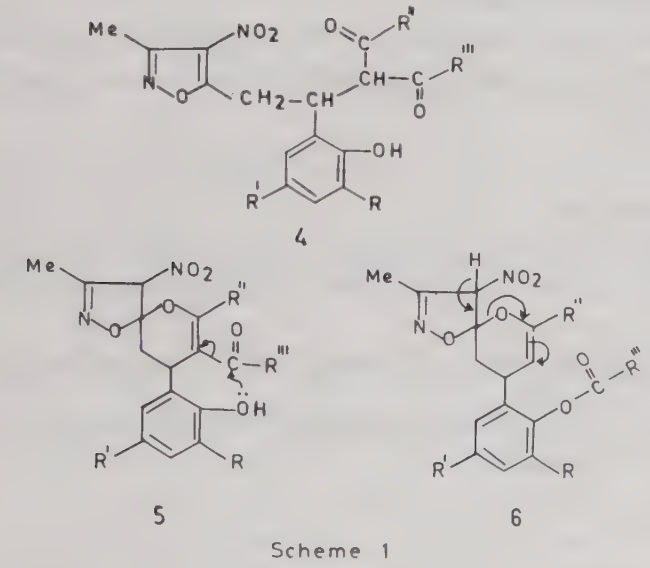
Table 1—Characterization Data of Michael Adducts (**3, 8** and **9**) and Cyclireduction Products (**7**)

| Compd No. | m.p. °C | Reaction time (hr) | Yield (%) | Mol formula | Found (%) (Calc.) | | |
|---|---|---|---|---|---|---|---|
| | | | | C | C | H | N |
| **3a** | 95 | 10 | 65 | $C_{22}H_{20}N_2O_6$ | 64.6 (64.7 | 4.8 4.9 | 6.7 6.8) |
| **3b** | 107 | 10 | 75 | $C_{23}H_{22}N_2O_7$ | 62.9 (63.0 | 4.9 5.0 | 6.2 6.3) |
| **3c** | 135 | 10 | 70 | $C_{22}H_{20}N_2O_6Br$ | 54.0 (54.0 | 4.1 4.0 | 5.6 5.7) |
| **3d** | 140 | 10 | 80 | $C_{22}H_{20}N_2O_6Cl$ | 58.9 (59.0 | 4.4 4.5 | 6.2 6.3) |
| **3e** | 160 | 10 | 65 | $C_{22}H_{18}N_2O_6Br_2$ | 46.5 (46.6 | 3.0 3.1 | 4.8 4.9) |
| **3f** | 124 | 4 | 60 | $C_{18}H_{20}N_2O_7$ | 57.3 (57.4 | 5.2 5.3 | 7.3 7.4) |
| **7a** | 238 | 3 | 55 | $C_{20}H_{18}N_2O_2$ | 75.3 (75.4 | 5.6 5.6 | 8.7 8.8 |
| **7b** | 175 | 3 | 60 | $C_{21}H_{20}N_2O_3$ | 72.3 (72.4 | 5.6 5.7 | 8.0 8.0) |
| **7c** | 230 | 3 | 50 | $C_{20}H_{17}N_2O_2$ | 60.1 (60.4 | 4.1 4.2 | 7.1 7.0) |
| **7d** | 177 | 2 | 65 | $C_{15}H_{16}N_2O_2$ | 70.1 (70.3 | 6.1 6.2 | 10.8 10.9) |
| **9a** | 117 | 3 | 60 | $C_{19}H_{22}N_2O_8$ | 56.0 (56.1 | 5.3 5.4 | 6.7 6.8) |
| **9b** | 120 | 2 | 70 | $C_{17}H_{17}N_3O_6$ | 56.7 (56.8 | 4.6 4.7 | 11.5 11.6) |




Scheme 1

port the assigned structure. The PMR and mass spectral data are in accordance with structure (**7**).

Michael addition of ethyl acetoacetate to **2** has been carried out in triethylamine by refluxing for 3-4 hr. Based on the chemical and spectral data the product of Michael additioin has been identified as 4-*o*-ethoxycarbonyloxyphenyl-5-(3-methyl-4-nitro-5-isoxazolyl)-2-pentanone (**8**). Neither the β-dicarbonyl system nor the phenolic hydroxyl is present in the product (insoluble in dil. alkali and no ferric colour). The PMR spectrum also confirms the conclusion (absence of exchangeable proton with $D_2O$).

Reduction of **8** with stannous chloride in conc. hydrochloric acid confirmed the migration during Michael reaction and led to 3,5-dimethyl-7-(*o*-hydroxyphenyl)-7, 8-dihydro- 6H-isoxazolo[7,8-*b*]azepines (**7d**) which was obtained earlier by the authors[2] by the reduction of **3f** under the same conditions. The IR spectrum of **7d** did not display any carbonyl absorption and exhibited ηOH in the region 3300-3200 $cm^{-1}$. Mass spectrum gave the molecular ion at *m/z* 256. In the PMR spectrum 3-$CH_3$ and 5-$CH_3$ signals were observed at δ 2.2 (*s*) and 1.8 (*s*), respectively. Five protons of two methylenes and one methine appeared as a complex multiplet in the region 2.4-3.5. That it is the carbethoxyl and not the acetyl group which has migrated during Michael addition is clearly proved by the structure of **7d**.

Contrary to the course of the two Michael additions described above, the interaction of **2** with diethyl malonate and ethyl cyanoacetate gave usual adducts ethyl α-carbethoxy-β-(*o*-hydroxyphenyl)-γ-(3-methyl-4-nitro-5-isoxazolyl)-*n*-butyrate (**9a**) and α-carbethoxy -β- (*o*-hydroxyphenyl) -γ-4-nitro-5-isoxazolyl)-*n*-butyronitrile (**9b**) respectively without involving intramolecular migration. These products were soluble in dil. NaOH solution and gave positive ferric reaction. The IR spectrum of the Michael adduct (**9a**) exhibited two important absorptions at 1725 (strong) and 3300 $cm^{-1}$ due to

ester carbonyl and hydroxyl respectively. The cyanide peak in **9b** appeared at 2200 $cm^{-1}$.

The reasons as to why the intramolecular migration is not observed when diethyl malonate and ethyl cyanoacetate are used as Michael donors, is presumably due to the fact that the Michael adducts (**9a, b**) are incapable of enolization and hence no spiro compound formation occurs. Consequently migration cannot take place.

**Experimental Procedure**

All melting points are uncorrected. Purity of the compounds was checked by TLC. IR spectra were run in KBr on a Perkin-Elmer 283 spectrophotometer ($\lambda_{max}$ in $cm^{-1}$), 90 MHz PMR spectra in $CDCl_3$ on a Varian EM-390 spectrometer using TMS as the internal reference (chemical shifts in δ, ppm) and the mass spectra on a Varian MAT CH-7 instrument at 70 eV.

*General procedure for Michael addition: Formation of adducts* (**3, 8, 9a** *and* **9b**)

3-Methyl-4-nitro-5-(*o*-hydroxystyryl)isoxazole (2.4 g, 0.01 mol), the Michael donor (4.86 g, 0.03 mol) and triethylamine (35 ml) were refluxed for 3 hr. After removal of triethylamine the residue was triturated with petroleum ether and finally decomposed in methanol, filtered and crystallised from methanol as colourless crystals; IR of **3a**: 1750 (−CO−OR), 1675 (−CO−R); PMR ($CDCl_3$): 2.38 (*s*, 3H, $OCOCH_3$), 2.45 (*s*, 3H, −isoxazole-$CH_3$), 3.6 (*d*, 2H, $-CO-CH_2-$), 3.8 (*d*, 2H, -isoxazole-$CH_2-$), 4.3 (*m*, 1H, Ar-CH) and 7.8 (*m*, 9H, ArH). PMR (100 MHz) of **9a**: 1.25 (*t*, 6H, $2\times COOCH_2-CH_3$ of 2.5 (*s*, 3H, isoxazole-$CH_3$), 3.45 (*q*, 4H, $2\times COOCH_2CH_3$), 3.6-4.5 (*m*, 4H, isoxazole-$CH_2-CH-CH<$), 6.25 (*bs*, 1H, OH, $D_2O$ washable) and 6.9-7.1 (*m*, 4H, ArH); PMR of **9b**: 1.3 (*t*, 3H, $-CO_2-CH_2-CH_3$), 2.64 (*s*, 3H, isoxazole-$CH_3$), 3.5 (*q*, 2H, $CO_2CH_2CH_3$); 3.3-4.6 (*m*, 4H, isoxazole-$CH_2-CH-CH<$), 6.4 (*bs*, 1H, OH, $D_2O$ washable), and 7.0-7.3 (*m*, 4H, ArH).

*Cyclireduction of Michael adducts to azepines* (**7**)

The Michael adducts (**3** or **8**, 4.08 g or 3.7 g, 0.01 mol), tin(II) chloride (12 g) and conc. HCl (15 ml) were heated together on a water-bath. Within a few minutes the reaction mixture became clear. After 0.5 hr crystalline compound began to separate. The heating was continued for further 3 hr, cooled, filtered and washed with water. Recrystallisation was effected from methanol-acetone and methanol respectively; PMR (DMSO-$d_6$) of **7a**: 2.3 (*s*, 3H, -isoxazole-$CH_3$), 2.5-3.6 (*m*, 5H, 6-$CH_2-$, 8-$CH_2-$ and CH); 6.8-8.0 (*m*, 11H, ArH), 9.9 (*bs*, 1H, −OH); MS of **7a**: *m/z* 318 ($M^+$); PMR of **7b**: 2.44 (*s*, 3H, -isoxazole-$CH_3$), 2.9-3.7 (*m*, 5H, 6-$CH_2-$, 8-$CH_2-$ and ⩾CH), 3.9 (*s*, 3H, −OMe), 5.8 (*s*, 1H, OH, $D_2O$ washable), 7.0-8.1 (*m*, 8H, ArH); $^{13}C$ NMR: 9.6 (isoxazole $CH_3$), 31 (⩾CH); 33 (8-$CH_2-$), 38 (6-$CH_2-$), 119 (C-1), 127 and 128 (C-3 and C-5 interchangeable), 130 (C-1″), 135 (C-3a), 143 (⩾*C*−OH), 160 (C-8a).

**Acknowledgement**

One of the authors (V V) is grateful to the CSIR, New Delhi, for the award of a junior research fellowship.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 731-735

# Thermal Transformations of Some 3-Acyl-2-oxo-2*H*-1-benzopyrans with Acid Anhydrides

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*Received* 5 *May* 1986; *revised and accepted* 6 *February* 1987

The reaction of 3-benzoyl- and 3-acetyl-2-oxo-2*H*-1-benzopyrans (**4** and **5**) with acid anhydrides in the presence of sodium acetate or triethylamine has been studied. With propionic, butyric and isobutyric acid anhydrides, **4** affords the rearrangement products **6** and **7**, dilactones (**8**) and benzyl esters (**9**), whereas with acetic anhydride **6a**, **10**, **11** and **12** are obtained. The reaction of **5** with acetic and propionic acid anhydrides affords **6e**, **8f** and **9f**. Conversion of **9c** into different products under acidic conditions has also been studied.

We have observed earlier[1,2] that the esters (**1**) of 2-oxo-2*H*-1-benzopyran-3-carboxylic acid under Perkin reaction conditions are changed into the corresponding esters (**3**) of 2-oxochroman-4-acetic acid with or without a substitution in position-3. A more detailed study[2] showed that this conversion represents a new molecular rearrangement, most probably taking place via an intramolecular reacylation of the initially formed adduct **2**. In this paper we report the results of a similar rearrangement of 3-acylated 2-oxo-2*H*-1-benzopyrans, the structural analogues of **1**.

We have found that in contrast to **1** the behaviour of 3-benzoyl- and 3-acetyl-2-oxo-2*H*-1-benzopyrans (**4** and **5**) towards the anhydrides of acetic, propionic, butyric and isobutyric acids in the presence of sodium acetate or triethylamine is more complicated.

The reaction of **4** with the above anhydrides in the presence of sodium acetate led mainly to the rearrangement products 3-substituted 2-oxo-4-phenacylchromans (**6**) and 1-substituted 2,5-dioxo-4-phenyl-1,4-dihydro-2*H*,5*H*-pyrano[3,4-*c*][1]-benzopyrans (**8**). However, in the presence of triethylamine the reaction products were **8** and 3-(1-acyloxybenzyl)-2-oxo-2*H*-1-benzopyrans (**9**). The interaction of **4** with acetic anhydride was an exception. The reaction when carried out in the presence of sodium acetate gave **6a** and 4-(2-acetoxystyryl)-2-oxo-2*H*-1-benzopyran (**10**); in the presence of triethylamine only **10** was formed. In the presence of sodium acetate the reaction of **4** with acetic anhydride also gave **11** and **12** in very small amounts. The yields of the main products obtained from **4** and acid anhydrides in the presence of sodium acetate or triethylamine are given in Table 1.

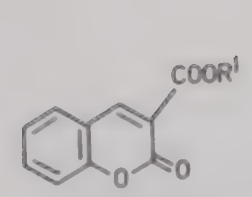
Table 1—Yields of the Reaction Products of **4** with Acid Anhydrides

| Type | Yields (%)* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | With sodium acetate | | | | With triethylamine | | | |
| | **a** | **b** | **c** | **d** | **a** | **b** | **c** | **d** |
| **6** | 12 | 38 | 10 | 24 | — | — | — | 16 |
| **7** | — | — | 14 | 51 | — | — | — | — |
| **8** | — | 28 | 44 | 15 | — | 46 | 41 | 32 |
| **9** | — | — | — | — | — | 32 | 24 | 25 |
| **10** | 16 | — | — | — | 8 | — | — | — |

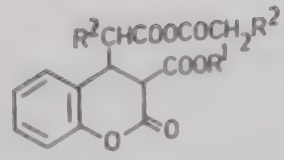
*Based on the amount of **4** consumed

It is very likely that the reaction of **4** involves the anionic precursor **13** arising by the addition of anhydride carbanion to **4**. Thus, compounds **6-9** can be formed by the transformations as shown in Scheme 1 wherein conversions occurring by the interaction of **4** with propionic anhydride are depicted.

The behaviour of the second model compound **5** was studied only towards the acetic and propionic anhydrides. The presence of an active methyl group in this compound determined essentially the course of the corresponding interactions. In both the cases large amounts of tarry products were formed. Only the rearrangement product 4-acetonyl-2-oxochroman (**6e**) was formed by the reaction of **5** with acetic anhydride in the presence of sodium acetate, and 3-(1-propionyloxyethyl)-2-oxo-2*H*-1-benzopyan (**9f**) and the dilactone **8f** were produced by the reaction with propionic anhydride in the presence of triethylamine. Besides **6e** in the first case, 2-oxo-2*H*-1-benzopyran (coumarin) was also isolated. It is most probably formed by the elimination of the mixed anhydride of acetylacetic acid and acetic acid from the direct precursor of **6e**.



1



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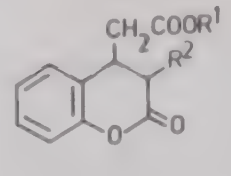

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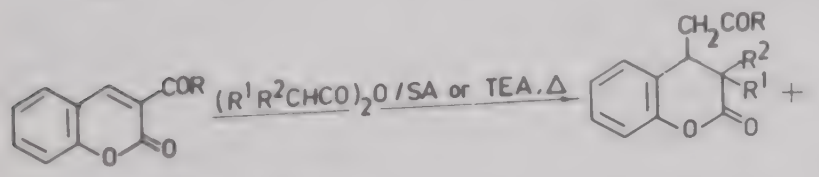
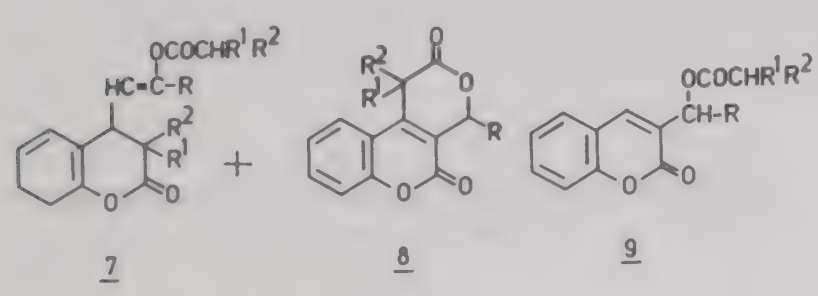
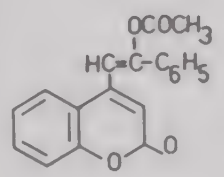


4: R=$C_6H_5$ SA=$CH_3COONa$
5: R=$CH_3$ TEA=$(C_2H_5)_3N$

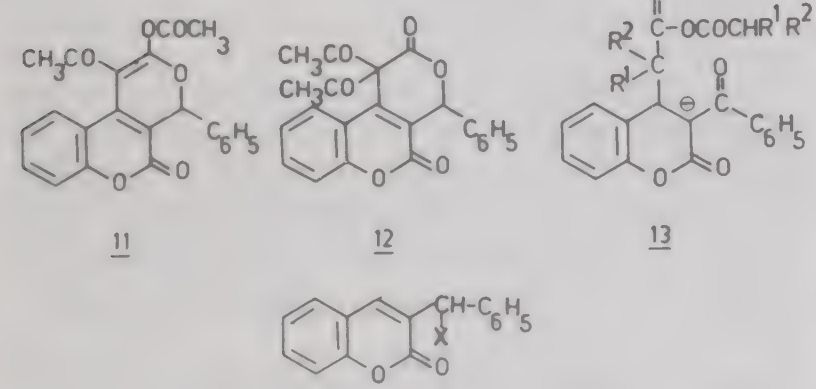


7 8 9

| | R | $R^1$ | $R^2$ |
|---|---|---|---|
| a | $C_6H_5$ | H | H |
| b | $C_6H_5$ | H | $CH_3$ |
| c | $C_6H_5$ | H | $C_2H_5$ |
| d | $C_6H_5$ | $CH_3$ | $CH_3$ |
| e | $CH_3$ | H | H |
| f | $CH_3$ | H | $CH_3$ |



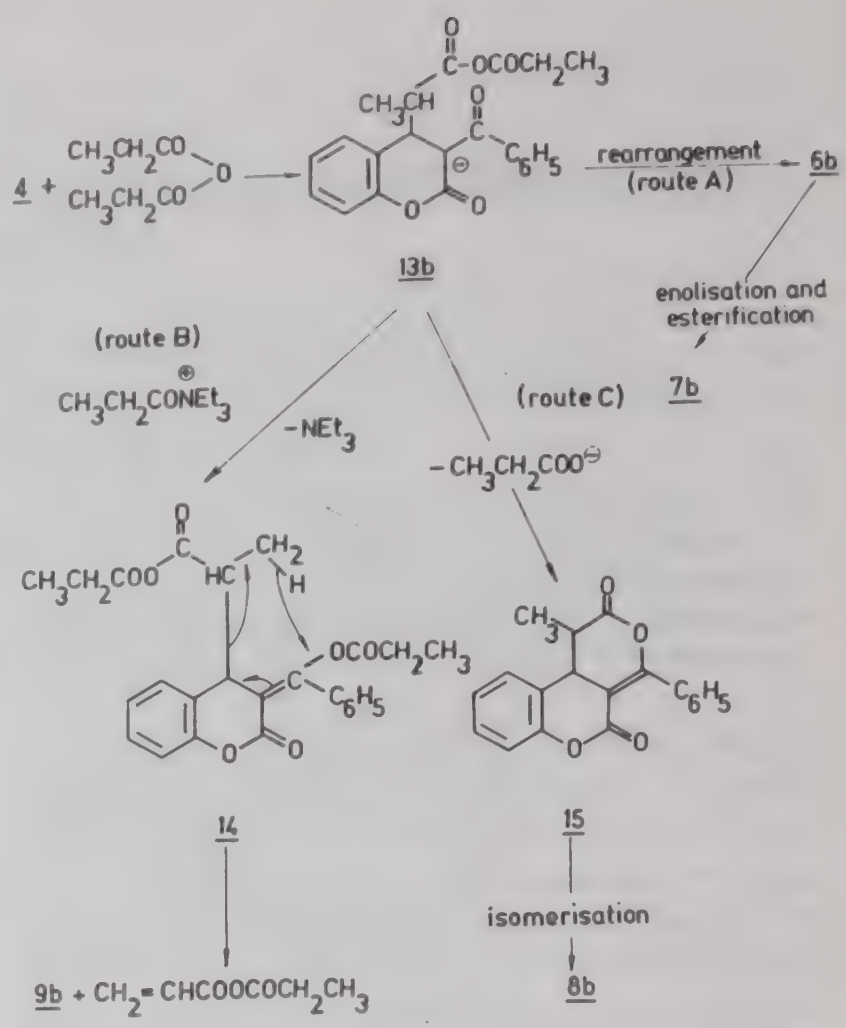
10



11 12 13



16 (X=OH)
17 (X=OCHO)




Scheme 1

The reaction products were identified by elemental analyses and IR and PMR spectral data. In some cases mass spectra were also applied.

Besides elemental analysis and spectral data, the structure of **9** was also established through the transformation of **9b** into a mixture of 3-(1-hydroxybenzyl)-2-oxo-2*H*-1-benzopyran (**16**) and 3-(1-chlorobenzyl)-2-oxo-2*H*-1-benzopyran by heating with hydrochloric acid[3], **9c** into **9a** by refluxing with gl. acetic acid and **9c** into a mixture of **16** and 3-(1-formyloxybenzyl)-2-oxo-2*H*-1-benzopyran (**17**) by heating with formic acid and concentrated sulphuric acid. The compounds **9a-d** were also prepared by refluxing 3-benzoyl-2-oxochroman wth acetic, propionic, butyric and isobutyric anhydrides in the presence of triethylamine[3].

## Experimental Procedure

Melting points are uncorrected. IR spectra in $CHCl_3$ or KBr were recorded on a Specord 71 IR or Perkin-Elmer 180 spectrophotometer ($\nu_{max}$ in $cm^{-1}$), PMR spectra on a Tesla 80 MHz or Bruker 250 MHz spectrometer using TMS as internal standard (chemical shifts in $\delta$, ppm), and mass spectra on a LKB 2091v or Jeol JMS-D300 spectrometer. Column chromatography and TLC were performed on Kieselgel 60 (Merck) and Merck silica gel 60 $F_{254}$ respectively.

3-Benzoyl- and 3-acetyl-2-oxo-2*H*-1-benzopyrans (**4** and **5**) were prepared according to literature methods[4,5].

## General Procedures

*Method-A* (*using sodium acetate*)

A mixture of equimolecular quantities (5 mmol) of 3-benzoyl- or 3-acetyl-2-oxo-2*H*-1-benzopyran (**4** or **5**) and sodium acetate in 5 ml of the appropriate anhydride was refluxed for 10 hr, excess of the anhydride removed under reduced pressure and 50 ml water added. The mixture was extracted

with chloroform (3 × 50 ml) and the combined extracts were washed with dil. sodium hydrogen carbonate solution, then with water and dried ($Na_2SO_4$). After removal of the solvent, the residue was purified by column chromatography on silica gel using hexane with increasing amount of ethyl acetate as eluant.

*Method-B* (*using triethylamine*)

The same procedure as in method-A was followed in this case.

2-*Oxo*-4-*phenacylchroman* (**6a**) (*Method-A*)

Yield 0.10 g (12%)† m.p. 90-92° (ethyl acetate-hexane), IR($CHCl_3$): 1692 (C=O, ketone), 1770 (C=O, lactone); PMR($CDCl_3$): 2.90 (*d*, 2H, $CH_2$), 3.26 (*d*, 2H, $CH_2$), 3.75-4.00 (*m*, 1H, H-4), 7.00-8.00 (*m*, 9H, Ar−*H*) (Found: C, 76.9; H, 5.2. $C_{17}H_{14}O_3$ requires C, 76.7; H, 5.3%).

3-*Methyl*-2-*oxo*-4-*phenacylchroman* (**6b**) (*Method-A*)

Yield 0.53 g (38%), colorless oil; IR($CHCl_3$): 1690 (C=O, ketone), 1765 (C=O, lactone); PMR($CDCl_3$): 1.20 (*d*, 3H, $CH_3$), 2.75-3.00 (*m*, 1H, H-3), 3.16 (*d*, 2H, $CH_2$), 3.25-3.65 (*m*, 1H, H-4), 6.93-7.88 (*m*, 9H, Ar−*H*) (Found: C, 77.4; H, 6.0. $C_{18}H_{16}O_3$ requires C, 77.1; H, 5.7%).

3-*Ethyl*-2-*oxo*-4-*phenacylchroman* (**6c**) (*Method-A*)

Yield 0.22 g (23%)†, colorless oil; IR($CHCl_3$): 1695 (C=O, ketone), 1770 (C=O, lactone); PMR($CCl_4$): 1.01 (*t*, 3H, $CH_3$), 1.26-1.79 (*m*, 2H, $CH_2CH_3$), 2.64 (*dt*, 1H, H-3, $J_{3,4}$=1.5 Hz), 3.11 (*d*, 2H, $CH_2$), 3.62 (*dt*, 1H, H-4), 6.87-7.92 (*m*, 9H, Ar−*H*) (Found: C, 78.0; H, 6.2. $C_{19}H_{18}O_3$ requires C, 77.5; H, 6.2%).

3,3-*Dimethyl*-2-*oxo*-4-*phenacylchroman* (**6d**)
*Method-A*

Yield 0.35 g (24%), m.p. 97-99° (ether-hexane); IR($CHCl_3$): 1690 (C=O, ketone), 1760 (C=O, lactone); PMR($CCl_4$): 1.22 and 1.33 [two *s*, 6H, >C($CH_3$)$_2$], 3.00-3.62 (*m*, 3H, $CH_2$ and H-4), 6.87-7.87 (*m*, 9H, Ar−*H*) (Found: C, 77.8; H, 6.2. $C_{19}H_{18}O_3$ requires C, 77.5; H, 6.2%).

*Method-B*

Yield 0.20 g (16%), m.p. 103-105° (ethanol); IR and PMR data were identical with those given above.

4-*Acetonyl*-2-*oxochroman* (**6e**) (*Method-A*)

Yield 0.22 g (23%)§, colorless oil; IR($CHCl_3$): 1720 (C=O, ketone), 1770 (C=O, . lactone); PMR($CCl_4$): 2.10 (*s*, 3H, $CH_3$), 2.60-2.80 (*m*, 4H, $CH_2$ + $CH_2$ of the lactone ring), 3.45-3.65 (*m*, 1H, H-4), 6.87-7.32 (*m*, 4H, Ar−*H*) (Found: C, 70.9; H, 5.9. $C_{12}H_{12}O_3$ requires C, 70.6; H, 5.9%).

4-(2-*Butyryloxystyryl*)-3-*ethyl*-2-*oxochroman* (**7c**)
(*Method-A*)

Yield 0.25 g (14%), colorless oil; IR($CHCl_3$): 1660 (C=C), 1760 (C=O, ester and lactone); PMR($CDCl_3$): 1.00 and 1.10 (two *t*, 6H, two $CH_3$), 1.50-2.05 (*m*, 4H, two $CH_2$), 2.33-2.93 (*m*, 3H, $CH_2$ and H-3), 3.80-4.05 (*m*, 1H, H-4), 5.65 (*d*, 1H, CH=C), 7.00-7.88 (*m*, 9H, Ar−*H*) (Found: C, 76.3; H, 6.6. $C_{23}H_{24}O_4$ requires C, 75.8; H, 6.6%).

4-(2-*Isobutyryloxystyryl*)-3,3-*dimethyl*-
2-*oxochroman* (**7d**) (*Method-A*)

Yield 0.92 g (51%), colorless oil; IR($CHCl_3$): 1665 (C=C), 1760 (C=O, ester and lactone); PMR($CCl_4$): 1.22-1.42 [*m*, 12H, >C($CH_3$)$_2$ and CH($CH_3$)$_2$], 2.62-3.00 (*m*, 1H, CH), 3.62 (*d*, 1H, H-4, $J_{H-4,\ CH=C} \approx 10.5$ Hz), 5.56 (*d*, 1H, CH=C), 6.87-7.67 (*m*, 9H, Ar−*H*) (Found: C, 76.0; H, 6.9. $C_{23}H_{24}O_4$ requires C, 75.8; H, 6.6%).

It was also obtained by heating **6d** (0.5 mmol) with sodium acetate (0.5 mmol) and isobutyric anhydride (3 ml) for 7 hr. The reaction mixture was worked-up as usual, yield 0.04 g (21%).

1-*Methyl*-2,5-*dioxo*-4-*phenyl*-1,4-*dihydro*-2*H*,5*H*-
*pyrano*[3,4-*c*][1]*benzopyran* (**8b**) *Method-A*

Yield 0.43 g (28%), m.p. 179-181° (ethyl acetate); IR($CHCl_3$): 1645 (C=C), 1725 (C=O, coumarin), 1745 (C=O, lactone); PMR($CDCl_3$): 1.37 (*d*, 3H, $CH_3$), 4.08 (*q*, 1H, CH), 6.67 (*s*, 1H, C*H*Ph), 7.19-7.66 (*m*, 9H, Ar−*H*) (Found: C, 74.0; H, 4.6. $C_{19}H_{14}O_4$ requires C, 74.4; H, 4.6%).

*Method-B*

Yield 0.70 g (46%), m.p. 179-181° (ethyl acetate). The IR and PMR data were identical with those given above; MS: *m/z* 306 ($M^+$, 38%), 277 ($M^+$ − 29; 100%).

It was also obtained by reacting **4** (1.25 g, 5 mmol) with propionic anhydride (5 ml) in the presence of pyridine (0.4 ml) following the same general procedure as in method A or B, yield 0.30 g (50%)†, m.p. 180-181° (ethyl acetate). Its IR and PMR data were identical with those given above.

1-*Ethyl*-2,5-*dioxo*-4-*phenyl*-1,4-*dihydro*-2*H*,5*H*-
*pyrano*[3,4-*c*][1]*benzopyran* (**8c**) *Method-A*

Yield 0.70 g (44%), m.p. 175-177° (ethyl acetate); IR($CHCl_3$): 1645 (C=C), 1725 (C=O, coum-

†Based on the amount of **4** or **5** assumed

rin), 1740 (C=O, lactone); PMR($CDCl_3$): 1.10 (*t*, 3H, $CH_3$), 1.37-1.80 (*m*, 2H, $CH_2$), 3.85-4.02 (*m*, 1H, CH), 6.72 (*s*, 1H, C*H*Ph), 7.25-7.62 (*m*, 9H, Ar−*H*) (Found: C, 74.8; H, 5.0. $C_{20}H_{16}O_4$ requires C, 75.0; H, 5.0%).

*Method-B*

Yield 0.65 g (41%), m.p. 175-177°, (ethyl acetate). Its IR and PMR data were identical with those given above.

1,1,*Dimethyl*-2,5-*dioxo*-4-*phenyl*-1,4,-*dihydro*-2*H*,5*H*-*pyrano*[3,4-*c*][1]*benzopyran* (**8d**)

*Method-A*

Yield 0.25 g (15%), m.p. 172-174° (ethanol); IR($CHCl_3$): 1635 (C=C), 1725 (C=O, lactone rings); PMR($CDCl_3$): 1.95 and 2.01 [two *s*, 6H, $>C(CH_3)_2$], 6.56 (*s*, 1H, C*H*Ph), 7.25-8.12 (*m*, 9H, Ar−*H*) (Found: C, 74.6; H, 5.2. $C_{20}H_{16}O4$ requires C, 75.0; H, 5.0%).

*Method-B*

Yield 0.45 g (32%)†, m.p. 172-174° (ethanol). Its IR and PMR data were identical with those given above.

1,4-*Dimethyl*-2,5-*dioxo*-1,4-*dihydro*-2*H*,5*H*-*pyrano*-[3,4-*c*][1]*benzopyran* (**8f**) (*Method-B*)

Yield 0.15 g (12%), m.p. 180-183° (ethanol); IR($CHCl_3$): 1645 (C=C), 1730 (C=O, lactone rings); PMR($CDCl_3$): 1.69 and 1.70 (two *d*, 6H, two $CH_3$), 4.04 (*q*, 1H, CHCO), 5.60 (*q*, 1H, CH−O), 7.17-7.67 (*m*, 4H, Ar−*H*) (Found: C, 69.0; H, 5.2. $C_{14}H_{12}O_4$ requires C, 68.8; H, 4.9%).

2-*Oxo*-3-(1-*propionyloxybenzyl*)-2*H*-1-*benzopyran* (**9b**) (*Method-B*)

Yield 0.50 g (32%), m.p. 110-112° (ethanol); IR($CHCl_3$): 1638 (C=C), 1720 (C=O, coumarin), 1740 (C=O, ester); PMR($CDCl_3$): 1.09 (*t*, 3H, $CH_3$), 2.33 (*q*, 2H, $CH_2$), 6.89 (*s*, 1H, C*H*Ph), 7.13-7.53 (*m*, 9H, Ar−*H*), 7.66 (*s*, 1H, H-4); MS: *m/z* 308 ($M^+$, 1.2%), 252 ($M^+ - 56$; 52%), 173 ($M^+ - 56, -79$; 100%) (Found: C, 74.2; H, 5.4. $C_{19}H_{16}O_4$ requires C, 74.0; H, 5.2%).

3-(1-*Butyryloxybenzyl*)-2-*oxo*-2*H*-1-*benzopyran* (**9c**) (*Method-B*)

Yield 0.30 g (24%)†, m.p. 77-79° (ether-hexane); IR($CHCl_3$): 1635 (C=C), 1720 (C=O, coumarin), 1740 (C=O, ester); PMR($CDCl_3$): 0.92 (*t*, 3H, $CH_3$), 1.45-1.90 (*m*, 2H, $CH_2$), 2.42 (*t*, 2H, $CH_2$), 6.92 (*s*, 1H, C*H*Ph), 7.17-7.55 (*m*, 9H, Ar−*H*), 7.74 (*s*, 1H, H-4) (Found: C, 74.9; H, 5.7. $C_{20}H_{18}O_4$ requires C, 74.5; H, 5.6%).

3-(1-*Isobutyryloxybenzyl*)-2-*oxo*-2*H*-1-*benzopyran* (**9d**) (*Method-B*)

Yield 0.35 g (25%)†, m.p. 105-106° (ethanol); IR($CHCl_3$): 1635 (C=C), 1720 (C=O, coumarin), 1740 (C=O, ester); PMR($CDCl_3$): 1.22 and 1.31 [two *d*, 6H, $>CH(CH_3)_2$], 2.57-2.91 (*m*, 1H, CH), 6.96 (*s*, 1H, C*H*Ph), 7.25-7.60 (*m*, 9H, Ar−*H*), 7.74 (*s*, 1H, H-4) (Found: C, 74.9; H, 5.7. $C_{20}H_{18}O_4$ requires C, 74.5; H, 5.6%).

*Hydrolysis of* **9c**

(*i*) *With gl.* $CH_3COOH$

A mixture of **9c** (0.20 g) and acetic acid (10 ml) was refluxed for 10 hr, excess of acid removed *in vacuo*, and 20 ml water added to it. The mixture was extracted twice with ether, and the combined extracts were washed successively with dil. $NaHCO_3$ solution and water, and dried ($Na_2SO_4$). Solvent was evaporated and the residue purified by column chromatography on silica gel using ethyl acetate-hexane mixtures (1:9 and 1:4) as eluants. From fractions 12-18, 0.10 g (50%) of the starting **9c** was isolated.

The fractions 20-22 gave 0.08 g (89%, based on **9c** consumed) of **9a**, m.p. 135-138° (ethyl acetate-hexane). Its IR and PMR data were identical with those of an authentic sample[3].

(*ii*) *With* 85% *HCOOH* − *conc.* $H_2SO_4$

To a mixture of **9c** (0.80 g, 2.5 mmol) and 85% formic acid (10 ml) was added conc. sulphuric acid dropwised under stirring and cooling in an ice-bath. After keeping the reaction mixture at room temperature for 2 hr it was poured in ice water and the resultant precipitate filtrated, washed with dil. $NaHCO_3$ solution and water and dried. It was chromatographed on a column of silica gel using ethyl acetate-hexane mixtures (1:19, 1:9 and 1:4) as eluants. The fractions 29-34 gave 3-(1-formyloxybenzyl)-2-oxo-2*H*-1-benzopyran (**17**), yield 0.35 g (50%), m.p. 104-106°; IR($CHCl_3$): 1635 (C=C), 1720 (C=O, coumarin), 1740 (C=O, ester); PMR($CDCl_3$): 7.05 (*s*, 1H, C*H*Ph), 7.25-7.50 (*m*, 9H, Ar−*H*), 7.77 (*s*, 1H, H-4), 8.22 (*s*, 1H, CHO) (Found: C, 73.0; H, 4.3. $C_{17}H_{12}O_4$ requires C, 72.8: H, 4.3%).

Fractions 35-40 gave 3-(1-hydroxybenzyl)-2-oxo-2*H*-1-benzopyran (**16**), yield 0.20 g (32%), m.p. 120-122°. Its IR and PMR data were identical with those of an authentic sample[3].

2-*Oxo*-3-(1-*propionyloxyethyl*)-2*H*-1-*benzopyran* (**9f**) (*Method-B*)

Yield 0.07 g (6%), m.p. 95-98° (ethanol); IR($CHCl_3$): 1632 (C=C), 1735 (C=O, coumarin

and ester); PMR($CDCl_3$): 1.15 (*t*, 3H, $CH_3$), 1.52 (*d*, 3H, $CH_3$), 2.42 (*q*, 2H, $CH_2$), 5.92 (*q*, 1H, CH), 7.17-7.55 (*m*, 4H, Ar−*H*), 7.64 (*s*, 1H, H-4) (Found: C, 68.5; H, 5.7. $C_{14}H_{14}O_4$ requires C, 68.3; H, 5.7%).

*4-(2-Acetoxystyryl)-2-oxo-2H-1-benzopyran* (**10**) *Method-A*

Yield 0.15 g (16%)†, m.p. 162-164° (ethanol); IR($CHCl_3$): 1650 (C=C), 1720 (C=O, coumarin), 1755 (C=O, ester); PMR($CDCl_3$): 2.07 (*s*, 3H, $CH_3$), 5.91 (*s*, 1H, H-3), 6.51 (*s*, 1H, CH=C), 7.25-7.75 (*m*, 9H, Ar−*H*) (Found: C, 74.3; H, 4.6. $C_{19}H_{14}O_4$ requires C, 74.4; H, 4.6%).

*Method-B*

Yield 0.07 g (8%)†, m.p. 161-163° (ethanol). Its IR and PMR data were identical with those given above.

*1,1-Diacetyl-2,5-dioxo-4-phenyl-1,4-dihydro-2H,5H-pyrano*[3,4-*c*][1]*benzopyran* (**12**) *and its isomer* (**11**) (*Method-A*)

**11**—Yield 0.09 g (8%), m.p. 200-202° (ethyl acetate); IR(KBr): 1720 (C=O, ketone and lactone), 1768 (C=O, ester); PMR($CDCl_3$): 1.74 and 2.44 (two *s*, 6H, two $CH_3$), 6.63 (*s*, 1H, C*H*Ph), 7.27-7.63 (*m*, 9H, Ar−*H*); MS: *m/z* 376 ($M^{+\cdot}$; 21%), 334 ($M^{+\cdot}-42$, 100%).

**12**—Yield 0.05 g (5%), m.p. 170-190° (mixed with **11**); IR(KBr): 1718 (C=O, ketone and lactone), 1741 (C=O, lactone); PMR($CDCl_3$): 1.92 and 2.30 (two *s*, 6H, two $CH_3$), 6.65 (*s*, 1H, C*H*Ph), 7.27-7.74 (*m*, 9H, Ar−*H*); MS: *m/z* 376 ($M^{+\cdot}$, 16%), 43 ($M^{+\cdot}-333$, 100%, $CH_3CO^{+\cdot}$).

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 736-738

# Action of Iodine Monochloride, Iodine Monobromide & Iodine on Aromatic Acetals

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*Received* 15 *September* 1986; *accepted* 5 *February* 1987

Photo-initiated action of ICl on aromatic acetals yields the corresponding esters and the parent aldehydes, and in the absence of light relatively low yield of esters is obtained. The reaction with IBr produces similar products but the effect of light is not noticeably felt. Iodine-catalyzed reaction results only in the formation of aldehydes under either conditions. The nature of solvent medium greatly affects the course of the reaction.

Lewis acid catalyzed reactions of aromatic acetals have been studied earlier in our laboratory[1,2], but the action of iodine and its interhalogen compounds on acetals do not seem to have been studied much. The interhalogen compounds are in effect, halogens although electronegativity differences render them some what more polar in character than the parent halogens[3]. As a result, they are less reactive than the parent halogens witgh respect to homolytic dissociation but more reactive with respect to heterolytic dissociation[4]. However, a few interhalogens are known to undergo effective photolytic fission[5]. A salient feature observed with these compounds is their bifunctional behaviour as halogenating agents[6,7] and as Lewis acids.[8] In the present study, an attempt has been made to investigate the influence of some of these compounds on aromatic acetals.

*Action of ICl on acetals*

Light-induced action of ICl on aromatic acetals in *n*-hexane produced esters as the major product along with the parent aldehydes (Table 1), and in the absence of light, the yield of the esters was poor. Similar reaction in 1,2-dichloroethane medium gave identical products, but the yield of ester was unaffectged by light. These striking features eloquently imply the possible homolytic and heterolytic type of fission in the system.

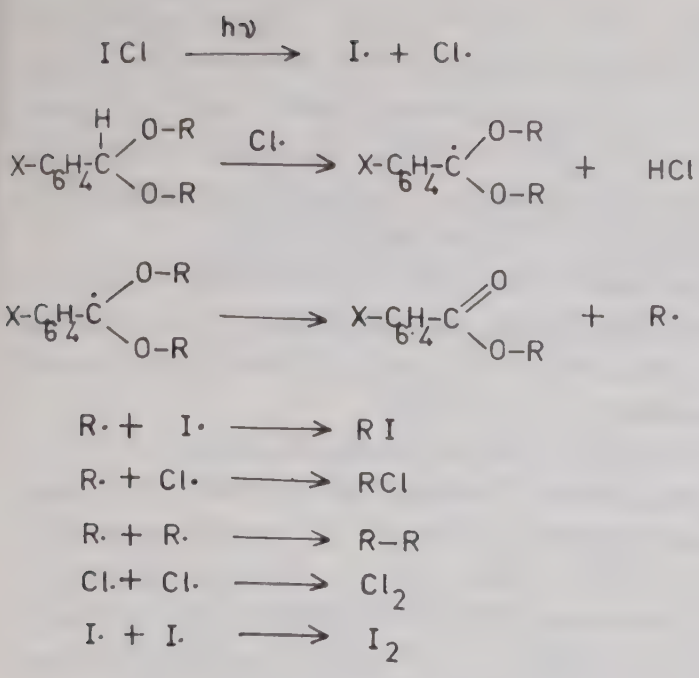
Acetals are relatively susceptible to radical attack on the C-H bond. Various reactions are known in which derivatives of the radicals are formed in good yields. An efficient splitting[5,10] of halogen atoms has been reported as the primary event in the photolysis of ICl. In the present study, under the influence of light such effective cleavage would make way for radical acetal formation. Eventually, the radical on subsequent cleavage would result in an ester as shown in Scheme 1. Identification of termination step products in the reaction mixture, adequately substantiate the present proposal. In favour of the proposed scheme, we observed a slow rate of formation of ester with deuterated acetal.

Homolytic fission of ICl needs photo initiation. Therefore, if reaction occurs in the absence of light, it would solely be due to heterolytic fission. In a solvent of high dielectric constant, the heterolytic fis-

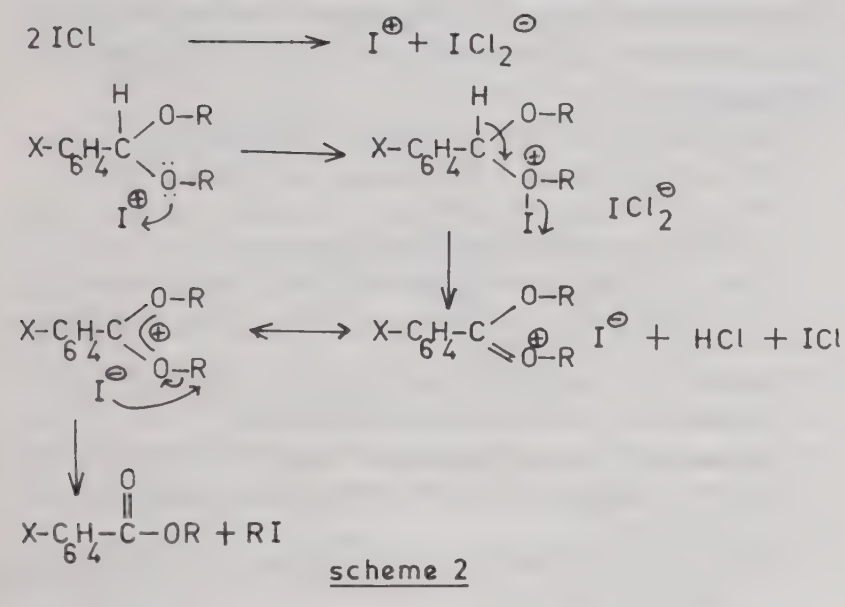
Table 1—Percentage Yields of Products and Product Distribution

| Acetal | ICl in presence of light (n-hexane) | | | ICl in absence of light (1,2-dichloroethane) | | | IBr (1,2-dichloroethane) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Net conversion (%) | Ester (%) | Aldehyde (%) | Net conversion (%) | Ester (%) | Aldehyde (%) | Net conversion (%) | Ester (%) | Aldehyde (%) |
| **1** | 82 | 76 | 24 | 61 | 18 | 82 | 79 | 79 | 21 |
| **2** | 84 | 73 | 27 | 63 | 16 | 84 | 83 | 77 | 23 |
| **3** | 87 | 70 | 30 | 65 | 15 | 85 | 85 | 73 | 27 |
| **4** | 83 | 64 | 36 | 72 | 26 | 74 | 94 | 83 | 17 |
| **5** | 92 | 78 | 22 | 49 | 8 | 92 | 69 | 26 | 74 |

**1**, benzaldehyde diethylacetal; **2**, benzaldehyde di-n-butylacetal; **3**, benzaldehyde di-isoamylacetal, **4**, *p*-methylbenzaldehyde di-*n*-butylacetal; and **5**, *p*-nitrobenzaldehyde di-*n*-butylacetal,
GLC yields were corrected for detector response factor and are the average of at least three injections.



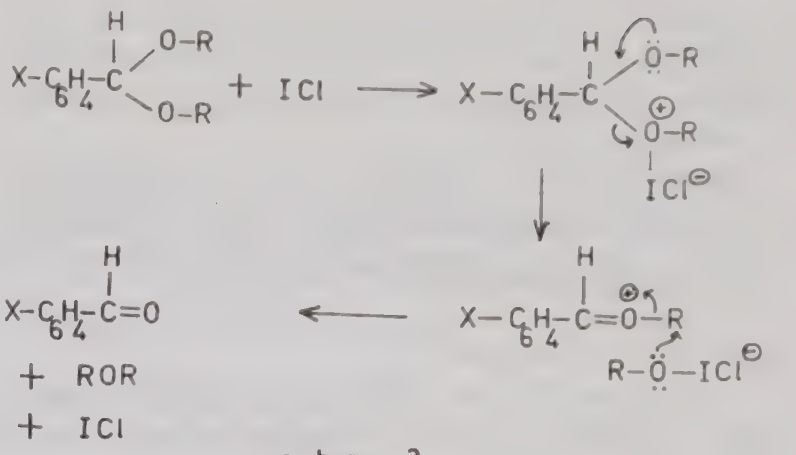
scheme 1



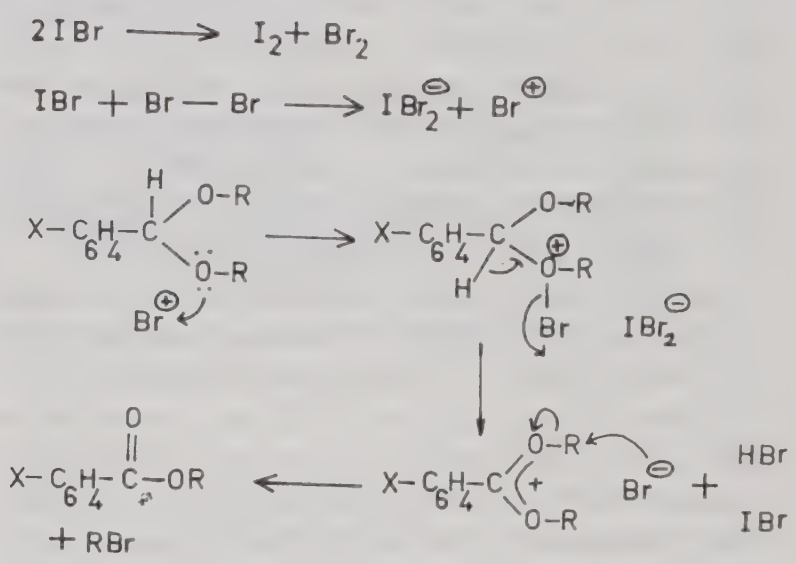
scheme 2

sion of ICl eclipses the homolytic process and under such conditions iodination occurs exclusively[4]. Evidence so far available reveal that heterolytic fission[4,11] of ICl leads to ionization of the type $2ICl \rightarrow I^+ + ICl_2^-$. Interaction of these ionized species with acetal would result in the formation of ester as shown in Scheme 2. This mechanism aptly coincides with the mechanism proposed by Deno and Potter[12] for oxidation of aromatic ethers by halogen. The valid evidences[13,14] of halogen-ether complex containing X-O bond further authenticates the present proposal.

In the presence of light, the yield of ester decreases as the dielectric constant of the medium increases. In the absence of light, the order reverses. This trend evidently proves the relative ease of homolytic fission and of heterolytic fission in solvents of low dielectric constants and high dielectric constants respectively. Further, isolation of polymer from methyl acrylate in the presence of ICl on irradiation reaffirms the formation of free radicals in the light-induced reaction.



scheme 3



scheme 4

The aldehyde formation could be explained on the basis of the fact that halogens and interhalogens exhibit an additional property, i.e. they act as electron acceptors forming $\sigma$-complexes[8,15] with a wide range of donor species. The acceptor strengths[16] follow the sequence; ICl > IBr > $I_2$. Hence, ICl would effectively form the $\sigma$-complex of the type described in the Scheme 3. The intermediate on further cleavage would yield the aldehyde. If the mechanism shown in Scheme 1 is really operative, alkyl ether should have been formed, which indeed been identified by GLC.

*Action of IBr on acetals*

Action of IBr on acetals yielded similar products as in the earlier case. But the yield of ester did not improve even in the presence of light. In addition, moderately polar solvents such as 1,2-dichloroethane greatly enhanced the formation of ester. These observations clearly indicate the fact that the reaction is mostly ionic in nature.

The IBr, corresponds closely in properties to ICl and generally acts as a brominating agent[4]. In the reaction, the possible reactive species $Br^+$ may be formed[17] by the action of free bromine on excess of Lewis acid IBr. Free bromine is probably formed by the dissociation[4,18] of IBr. Even in a solvent of low dielectric constant like $CCl_4$, IBr has been shown to

dissociate[19] to the extent of 9.5%. To account for the formation of ester, a probable mechanism shown in Scheme 4 has been put forward. This is in confirmity with the earlier report.[12]

The formation of aldehyde could be explained on the basis of $\sigma$-complex forming[4,16] ability of IBr with the alkoxy group as delineated in Scheme 3.

**Action of $I_2$ on acetals**

The action of $I_2$ on acetals gave only the aldehydes, a common product found in the earlier cases. The absence of ester can be expected from its inability to produce an electrophile $I^+$ in the absence of strong acids.[20] Moreover, halogenation by means of a homolytic pathway is also not possible, because under the present photolytic conditions, $I_2$ may not dissociate.[21] As a result $I_2$ could produce only the parent aldehyde through the usual complex formation[4,16] similar to that described in Scheme 3.

The reaction of acetals with ICl (in the presence of light) and IBr brought out almost identical total conversion (Table 1). This feature evidently intimates the efficient splitting of ICl on photolysis in solvents of low dielectric constants and effective dissociation of IBr in solvents of high dielectric constants. Conductivity and electrolysis measurements have shown low degree of ionization[4,11] of ICl. These facts are in accord with the poor yield of ester in the absence of light. Gradual increase of aldehyde from acetal **1** to **3** reflects the possible better leaving behaviour of the alkoxy group as we go from ethyl to isobutyl, induced by $\sigma$-complex formation. Acetals having electron releasing substituents would favour the formation of carbonium ion (Schemes 2 and 4), while the electron withdrawing substituents would inhibit such formation. In accordance with this fact, we obtained relatively higher yield of ester from acetal **4** and low yield from **5**. However, the free radical intermediate would be stabilized by the electron withdrawing substituent; this is reflected in the higher yield of ester from acetal **5**.

**Experimental Procedure**

Acetals were prepared by the described procedures[22,23] and characterized by IR and PMR data. Refractive indices and boiling points of the acetals were compared with reported values. ICl and IBr were prepared by adopting the established methods[24,25].

A typical experiment carried out under perfectly day condition is described below. To a suspension of the catalyst (0.1 mol) in freshly distilled solvent (100 ml) was added a solution of acetal (0.1 mol) solvent (100 ml) dropwise with stirring during 15 min. After 1 hr, the reaction mixture was neutralised with ice-cold 10% aq sodium bisulfite and washed well with water. The organic layer was dried ($Na_2SO_4$) and the products from this layer were separated by column chromatography and TLC, and characterized by IR and PMR spectral data. Identification and the relative percentage of the products were determined with the help of GLC.

Photochemical reaction was conducted in an all glass apparatus using tungsten lamp as irradiation source. Nitrogen gas was purged during the course of the reaction.

PMR spectra were recorded in either $CCl_4$ or $CDCl_3$ on a Varian T-60 or Varian HA-100D using TMS as an internal standard. IR spectra were obtained on a Perkin-Elmer 599 or Perkin-Elmer 781 spectrophotometer. GLC was performed on a Toshniwal $RLO_4$ (3 mm × 2.5 m) SS column packed with 5% SE 30 on chromosorb W-HP.

All chemicals used were of AR grade. Column chromatography and TLC were performed on silica gel supplied by BDH or Acme Synthetic Chemicals.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 739-743

# Heterocyclic Systems Containing Bridgehead Nitrogen Atom : Part LXI—Facile Synthesis of Spiro[cyclooctane-1,3′(4′*H*)-[2*H*]thiazolo-[3,2-*b*]-*s*-tetrazine], a New Heterocyclic System

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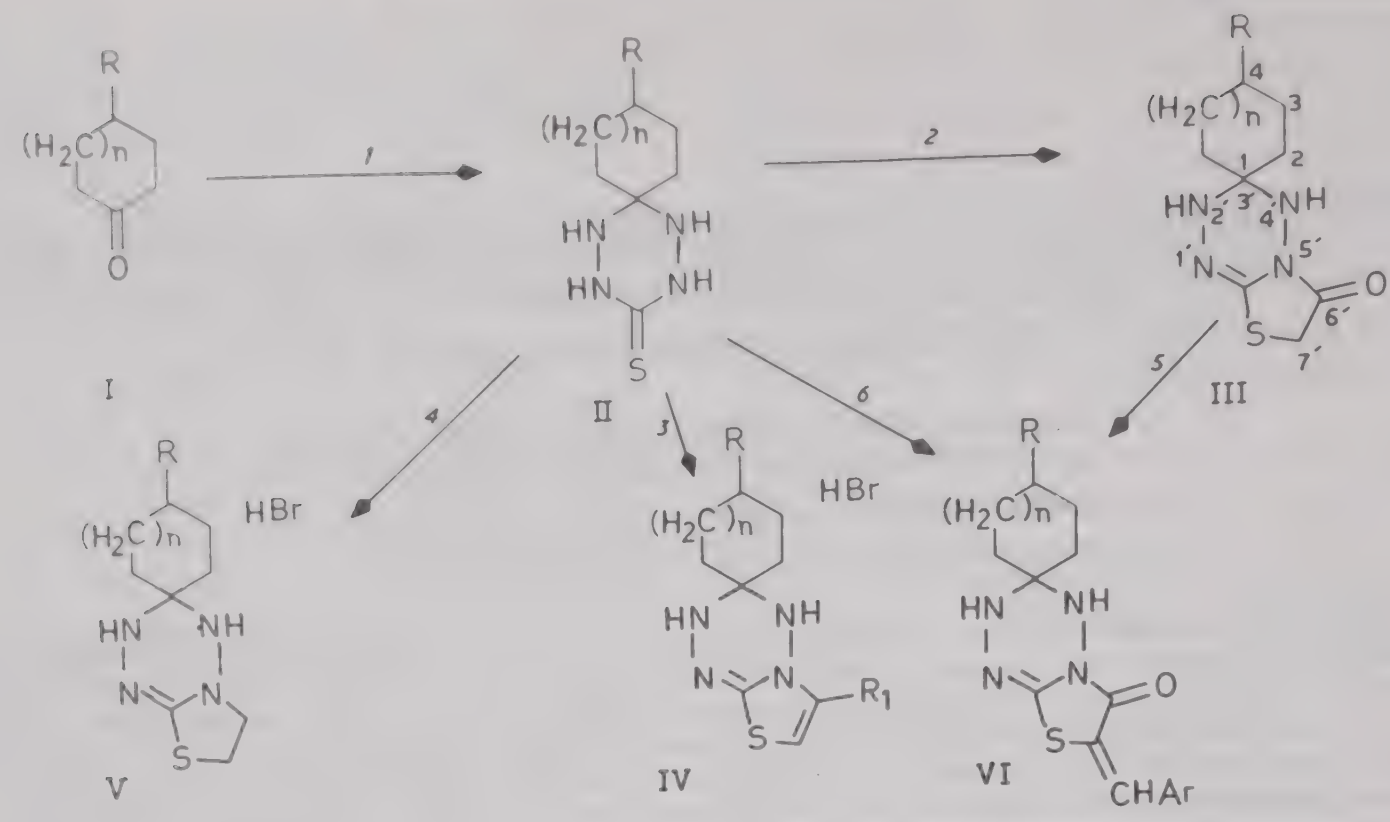
*Received* 22 *September* 1986; *accepted* 21 *January* 1987

9,10,12,13-Tetraazaspiro[5,7]tridecane-11-thione (IIc) and 4-methyl-7,8,10,11-tetraazaspiro[5,5]undecane-9-thione (IIe) on reaction with chloroacetic acid yield 6′(7′*H*)-oxospiro[cyclooctane-1,3′(4′*H*)[2 *H*]thiazolo[3,2-*b*]-*s*-*tetrazine*] (IIIc) and 4-methyl-6′(7′*H*)-oxospiro[cyclohexane-1,3′(4′*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine] (IIIe) respectively. The thiones (IIc,e) on condensation with α-halogenoketones furnish 6′-aryl spiro[cyclooctane-1,3′(4′*H*)-[2*H*]thiazolo-[3,2-*b*]-*s*-tetrazine] hydrobromide (IVc) and 4-methyl-6′-arylspiro[cyclohexane-1,3′(4′*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine] hydrobromide (IVe) respectively. IIe on reaction with 1,2-dibromoethane gives 4-methyl-6′,7′-dihydrospiro-[cyclohexane-1,3′(4′*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine] hydrobromide (Ve). Arylidinethiazolidinones (VIc,e) have been obtained by two routes. Mass fragmentation pattern of 6′(7′*H*)-oxospiro[cycloalkane-1,3′(4′*H*)-[2*H*]-thiazolo[3,2-*b*]-*s*-tetrazine] (IIIa-d,f,g) has also been studied. Compounds IIIc-VIc represent a novel and hitherto unknown heterocyclic system.

In a research programme designed towards the synthesis of novel and hitherto unknown hetrocyclic systems containing spiro linkage, we reported the synthesis of IIIa[1], IIIb[2], IIId[3], IIIf[4] and IIIg[5] containing 5:6:12, 5:6:10, 5:6:7, 5:6:6 and 5:6:5 ring systems respectively. We now wish to report the synthesis and characterisation (IR, PMR and mass) of a hitherto unknown 5:6:8 ring system namely spiro[cyclooctane-1,3′(4′*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine] (Scheme 1).

9,10,12,13-Tetraazaspiro[5,7]tridecane-11-thione (IIc) was obtained by the condensation of cyclooctanone (Ic) with thiocarbohydrazide following the method reported by Lamon[6]. The reaction of IIc with chloroacetic acid and α-halogenoketones resulted in 6′(7′*H*)-oxospiro[cyclooctane-1,3′(4′*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine] (IIIc) and 6′-arylspiro[cyclooctane-1,3′(4′*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine] hydrobromides (IVc) respectively. Similarly, IIe obtained by the condensation of 4-methylcyclohexanone (Ie) with thiocarbohydrazide, when reacted with chloroacetic acid, α-halogenoketones and 1,2-dibromoethane furnished 4-methyl-6′(7′*H*)-oxospiro[cyclohexane-1,3′(4′*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine] (IIIe), 6′-aryl-4-methylspiro[cyclohexane-1,3′(4′*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine] hydrobromides (IVe) and 4-methyl-6′,7′-dihydrospiro[cyclohexane-1,3′(4′*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine] hydrobromide (Ve) respectively.

7′-Arylidene-6′(7′*H*)-oxospiro[cyclooctane-1,3′(4′*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine] (VIc) and 7′-arylidene-4-methyl-6′(7′*H*)-oxospiro[cyclohexane-1,3′(4′*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine] (VIe) were prepared by two routes. In the first route, the thiazolidinones (IIIc,e) were condensed with aldehydes while in the second route the thiones (IIc,e) were heated with ethyl chloroacetate and aldehydes in the presence of pyridine and piperidine. The structures of thiazolidinones (IIIc,e), arylidenethiazolidinones (VIc,e), thiazoles (IVc,e) and dihydrothiazole (Ve) have been characterized by spectral data (IR, PMR and mass). The parent thiazolidinones (IIIc,e) absorbed at 1720 $cm^{-1}$ (>N-C=O) but the unsaturation at 7′-position being in conjugation with 6-carbonyl as in the case of arylidenethiazolidinones (VIc,e) showed bathochromic shifts[7]. The carbonyl absorption bands appeared at 1695, 1710, 1700, 1695, 1700, 1690, 1700 and 1700 $cm^{-1}$ in the IR spectra of VIc (Ar = 3,4-$(MeO)_2C_6H_3$, Ar = *o*-$ClC_6H_4$, Ar = *p*-$ClC_6H_4$ Ar = *p*-$Me_2NC_6H_4$) and VIe (Ar = 3,4-$(MeO)_2C_6H_3$, Ar = *o*-$ClC_6H_4$, Ar = *m*-$ClC_6H_4$ and Ar = $C_6H_5$) respectively. Lack of an absorption in the region 1660-1700 $cm^{-1}$ in the IR spectra of IVc,e showed the absence of a carbonyl group suggesting thereby cyclic structure for IV. The PMR signals at 7.09 (1H, *s*, $C_7$-H), 7.18 (1H, *s*, $C_7$-H), 7.07 (1H, *s*, $C_7$-H), 6.89 (1H, *s*, $C_7$-H), 7.05 (1H, *s*, $C_7$-H), 7.05 (1H, *s*, $C_7$-H) exhibited by IVc ($R_1$ = p-$BrC_6H_4$, $R_1$ = *m*-$O_2NC_6H_4$, $R_1$ = $C_6H_5$) and IVe ($R_1$ = *p*-$BrC_6H_4$, $R_1$ = *p*-$ClC_6H_4$, $R_1$ = $C_6H_5$ provided support to the cyclic structure. The structures IIIc,e and Ve have been confirmed by PMR and mass spectral data (vide Experimental).

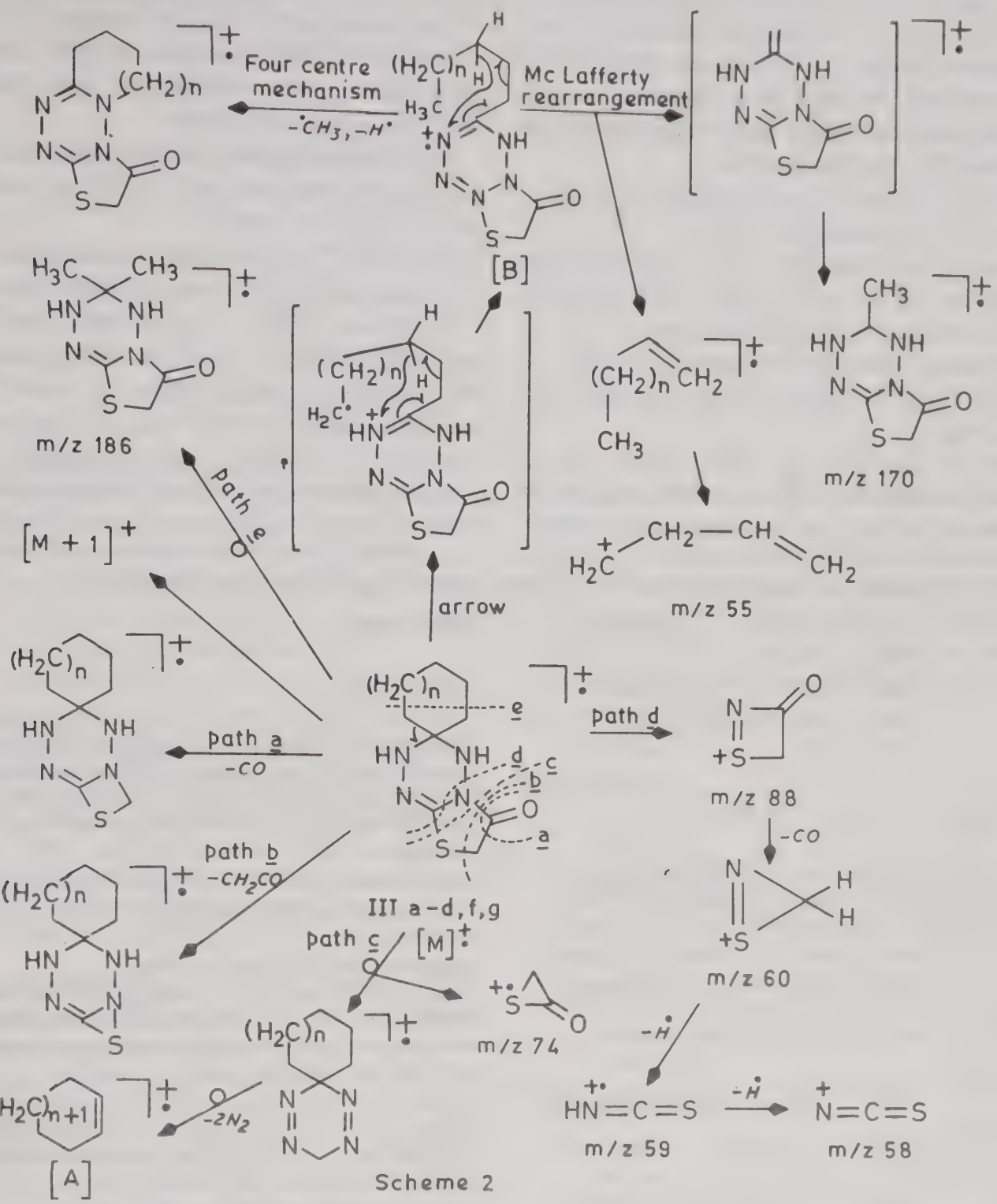



1. $H_2NNHCSNHNH_2$ ;
2. $ClCH_2CO_2H$ , anhyd. NaOAc ;
3. $R_1COCH_2Br$ ;
4. $BrCH_2CH_2Br$ ;
5. ArCHO , anhyd. NaOAc;
6. $ClCH_2CO_2Et$ , pyridine , ArCHO , piperidine;

a, R = H , n = 7
b, R = H , n = 5
c, R = H , n = 3
d, R = H, n = 2
e, R = $CH_3$, n = 1
f, R = H , n = 1
g, R = H , n = 0

Scheme 1

Although the mass fragmentation of thiazoles[8–10] and tetrazines[11–16] have been well-documented no such work on the thiazolotetrazine system has been reported so far. We have, therefore, studied the behaviour of 6′(7′-*H*)oxospiro[cycloalkane-1,3′(4′*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine] (IIIa-d,f,g) under electron impact (Scheme 2). In the mass spectra of IIIa-d, the molecular ion peaks are not the base peaks showing thereby that IIIa-d are not stable under electron impact. On the other hand, IIIf-g are stable and exhibit the molecular ion peaks as the base peaks. This is quite understable as the cyclopentane ring as in IIIg and cyclohexane ring as in IIIf are more stable than the other cycloalkane rings (cf.IIIa-d). The ions $[M-1]^+$, $[M-S]^+$ and [M-SH] are not found in the mass spectra of IIIa-d,f,g. The mass fragmentation of IIIa-d,f,g follow several pathways involving the fission of one or more bonds of thiazolidinone, tetrazine or cycloalkane ring. The molecular ion peaks lose elements of CO, $CH_2CO$ and $SCH_2CO$ paths via *a*, *b* and *c*, resulting in the formation of $[M-CO]^+$ and $[M-CH_2CO]^+$ and $[M-SCH_2CO]^+$ ions, respectively. The ion $[M-SCH_2CO]^+$ on further loss of two molecule of nitrogen with rearrangement furnishes cycloalkene ion [A] in all cases. The ion $[SCH_2CO]^+$ itself appears at *m/z* 74. The 1,2-thiazetidonyl cation at *m/z* 88, formed by the loss of CO(path *d*) from the molecular ion gives ion at *m/z* 60 which in turn on successive loss of two hydrogen radicals gives $HN^+ \equiv C - S$ at *m/z* 59 and N = C = S at *m/z* 58. The molecular ion through the cleavage of one bond of the cycloalkane ring (fish hook arrow) yields ion [B] which undergoes McLafferty rearrangement to give ions at *m/z* 170 and $CH_3(CH_2)_n RC = CH_2^{7+}$. The latter ion undergoes usual cleavage to produce various fragmented ions including ion $CH_2CH_2CH = CH_2$ at *m/z* 55. The ion at *m/z* 55 appears as the base peak in the case of IIIb d. (The formation of *m/z* 55 from IIIg through this reaction is structurally not possible). The rearranged ion [B] loses methyl and hydrogen radicals through four-centre mechanism furnishing the ion $[M-CH_4]^+$. It is interesting to note that in the cas eof spirododecane (IIIa) and spirodecane (IIIb) the fragmented ions $C_6H_{12}^+$ (appearing at *m/z* 84, 7.62%) and $C_4H_8^+$ (appearing at *m/z* 56, 22.8%) are respectively eliminated to give ion *m/z* 226 in 24.5% and 30.7% abundance. The ion at *m/z* 226 behaves like the parent thiazolidinone (IIIf) as evident from the frgment ions similar to those observed in the case of IIIf. The ion at *m/z* 186 is obtained through the pathway *e* from IIIa-d in varying abundance, *m/z* 186 ion




Scheme 2

being the base peak in IIIa while the abundance per cent is drastically decreased in IIIb-d. This ion is not observed in IIIf,g containing cyclohexane and cyclopentane rings, respectively. In this respect IIIa having a 12-membered ring behaves differently than IIIb-d,f,g.

## Experimental Procedure

Melting points were determined in a sulphuric acid bath and are uncorrected. The TLC was performed on silica gel plates using benzene-acetone (3:1) as an irrigant. IR spectra were recorded in nujol mull on a Beckman IR-20 spectrophotometer ($\nu_{max}$ in $cm^{-1}$) and PMR spectra on a Perkin-Elmer 90 MHz spectrometer in $CDCl_3$ and/or TFA using TMS as an internal standard (chemical shifts in $\delta$, ppm). Mass spectra were scanned on a Hitachi RMU-6D instrument at 70 eV.

9,10,12,13-*Tetraazaspiro*[5,7]*tridecane*-11-*thione* (*IIc*)

Cyclooctanone (Ic; 12.6 g, 0.1 mol) in ethanol (30 ml) was added dropwise under stirring to a solution of thiocarbohydrazide (10.6 g, 0.1 mol) in hot water (200 ml). The product began to precipitate during the course of addition. The reaction mixture was kept overnight and the white solid, thus obtained, was filtered, washed well with dil. ethanol and air-dried.

4-*Methyl*-7,8,10,11-*tetraazaspiro*[5,5]*undecane*-9-*thione* (*IIe*)

IIe was prepared from 4-methylcyclohexanone (Ie; 11.2 g, 0.1 mol) and thicarbohydrazide (10.6 g, 0.1 mol) following the above procedure.

6′(7′*H*)-*Oxospiro*[*cyclooctan*-1,3′(4′*H*)-[2*H*]*thiazolo*[3,2-*b*]-*s*-*tetrazine*] (*IIIc*)

A mixture of IIc (2.14 g, 0.01 mol), chloroacetic

acid (0.95 g, 0.01 mol) and anhydrous sodium acetate (0.82 g, 0.01 mol) in anhydrous ethanol (50 ml) was heated, under reflux, for 5 hr. The reaction mixture was cooled and the solid, thus obtained, was filtered, washed well with water and crystallized from ethanol to give IIIc as white needles.

*4-Methyl-6′(7′H)-oxospiro[cyclohexane-1,3′(4′H)-[2H]thiazolo[3,2-b]-s-tetrazine] (IIIe)*

IIIe was prepared from IIe (2.0 g, 0.01 mol) and chloroacetic acid (0.94 g, 0.01 mol) following the above method (white needles from ethanol).

*6′-p-Bromophenyl-spiro[cyclooctane-1,3′(4′H)-[2H]thiazolo[3,2-b]-s-tetrazine] hydrobromide (IVc, $R_1$ = p-$BrC_6H_4$)*

A mixture of IIc (1.07 g, 0.005 mol) and *p*-bromophenacyl bromide (1.39 g, 0.005 mol) in anhydrous ethanol (40 ml) was heated, under reflux, for 15 min. The reaction mixture was cooled to room temperature and the resultant solid, thus obtained, was filtered, washed well with water and crystallized from ethanol to give IVc ($R_1$ = *p*-$BrC_6H_4$) as white crystals.

In a similar manner, other compounds of the series IV were prepared and their characterization data are recorded in Table 1.

*4-Methyl-6′,7′-dihydrospiro[cyclohexane-1,3′(4′H)-[2H]thiazolo[3,2-b]-s-tetrazine] hydrobromide (Ve)*

A mixture of IIe (2.0 g, 0.01 mol) and 1,2-dibromoethane (1.88 g, 0.01 mol) in anhydrous ethanol (50 ml) was heated, under reflux, on a steam-bath for 6 hr. The reaction mixture was concentrated and kept overnight. The solid, thus separated, was filtered, washed well with water and finally crystallized from ethanol to give Ve as cream coloured granules.

Table 1—Characterization Data of Compounds IIc,e, IIIc,e, IVc,e, Ve and VIc,e

| Compd ($R_1$ or Ar) | m.p. (°C) | Yield (%) | Mol. formula* | PMR ($\delta$ scale) |
|---|---|---|---|---|
| IIc | 180 | 84 | $C_9H_{18}N_4S$ | |
| IIe | 182 | 85 | $C_8H_{16}N_4S$ | |
| IIIc | 120 | 63 | $C_{11}H_{18}N_4SO$ | ($CDCl_3$): 1.48 (6H, *m*, $C_4$-, $C_5$- and $C_6$-$CH_2$ of cyclooctane moiety), 1.84 (4H, *m*, $C_3$- and $C_7$-$CH_2$ of cyclooctane moiety), 2.53 (4H, *m*, $C_2$- and $C_8$-$CH_2$ of cyclooctane moiety), 3.72 (2H, *s*, $SCH_2$), 4.61 (2H, *bs*, 2 × NH, disappeared on deuterium exchange) |
| IIIe | 140 | 37 | $C_{10}H_{16}N_4SO$ | ($CDCl_3$): 0.97 (3H, *d*, $CH_3$), 1.91 (8H, *m*, $C_2$-, $C_3$-, $C_5$- and $C_6$-$CH_2$ of cyclohexane moiety), 3.38 (1H, *m*, $C_4$-H of cyclohexane moiety), 3.73 (2H, *s*, $SCH_2$), 4.41 (2H, *bs*, 2 × NH, disappeared on deuterium exchange). |
| IVc ($R_1$ = *p*-$BrC_6H_4$) | 195 | 51 | $C_{17}H_{22}N_4SBr_2$ | (TFA): 1.69 (6H, *m*, $C_4$-, $C_5$- and $C_6$-$CH_2$ of cyclooctane moiety), 2.16 (4H, *m*, $C_3$- and $C_7$-$CH_2$ of cyclooctane moiety), 3.05 (4H, *m*, $C_2$- and $C_8$-$CH_2$ of cyclooctane moiety), 7.09 (1H, *s*, $C_7$-H), 7.65 (4H, $AB_q$, ArH, $J_{AB}$ = 9 Hz). |
| IVc ($R_1$ = *m*-$O_2NC_6H_4$) | 185 | 28 | $C_{17}H_{22}N_5SO_2Br$ | (TFA): 1.67 (6H, *m*, $C_4$-, $C_5$- and $C_6$-$CH_2$ of cyclooctane moiety), 2.15 (4H, *m*, $C_3$- and $C_7$-$CH_2$ of cyclooctane moiety), 3.12 (4H, *m*, $C_2$- and $C_8$-$CH_2$ of cyclooctane moiety), 7.18 (1H, *s*, $C_7$—H), 7.85-8.60 (4H, *m*, ArH). |
| IVc ($R_1$ = $C_6H_5$) | 180 | 38 | $C_{17}H_{23}N_4SBR$ | (TFA): 1.70 (6H, *m*, $C_4$-, $C_5$- and $C_6$-$CH_2$ of cyclooctane moiety), 2.18 (4H, *m*, $C_3$- and $C_7$-$CH_2$ of cyclooctane moiety), 3.09 (4H, *m*, $C_2$- and $C_8$-$CH_2$ of cyclooctane moiety), 7.07 (1H, *s*, $C_7$-H), 7.61 (5H, *bs*, $C_6H_5$). |
| IVe ($R_1$ = *p*-$BrC_6H_4$) | 180 | 23 | $C_{16}H_{20}N_4SBr_2$ | (TFA + $CDCl_3$): 1.01 (3H, *d*, $CH_3$), 2.19 (9H, *m*, $C_2$-, $C_3$-, $C_5$- and $C_6$-$CH_2$ of cyclohexane moiety and $C_4$-H of cyclohexane moiety), 6.89 (1H, *s*, $C_7$-H), 7.58 (4H, $AB_q$, Ar-H, $J_{AB}$ = 8 Hz). |
| IVe ($R_1$ = *p*-$ClC_6H_4$) | 170 | 31 | $C_{16}H_{20}N_4SBrCl$ | (TFA): 1.06 (3H, *d*, $CH_3$), 2.33 (9H, *m*, $C_2$-, $C_3$-, $C_5$- and $C_6$-$CH_2$ of cyclohexane moiety and $C_4$-H of cyclohexane moiety), 7.05 (1H, *s*, $C_7$-H), 7.54 (4H, *m*, Ar-H). |
| IVe ($R_1$ = $C_6H_5$) | 160 | 52 | $C_{16}H_{21}N_4SBR$ | (TFA): 1.06 (3H, *d*, $CH_3$), 2.37 (9H, *m*, $C_2$-, $C_3$-, $C_5$- and $C_6$-$CH_2$ of cyclohexane moiety and $C_4$-H of cyclohexane moiety), 7.05 (1H, *s*, $C_7$-H), 7.59 (5H, *s*, $C_6H_5$). |
| Ve | 172 | 52 | $C_{10}H_{19}N_4SBr$ | (TFA + $CDCl_3$): 1.05 (3H, *d*, $CH_3$), 2.23 (8H, *m*, $C_2$-, $C_3$-, $C_5$- and $C_6$-$CH_2$ of cyclohexane moiety), 3.35 (1H, *m*, $C_4$-H of cyclohexane moiety), 3.63 (2H, *t*, $SCH_2$), 4.32 (2H, *t*, $NCH_2$). |
| VIc (Ar = 3,4-$(MeO)_2C_6H_3$) | 130 | 53 | $C_{20}H_{26}N_4SO_3$ | — |
| VIc (Ar = *o*-$ClC_6H_4$) | 165 | 53 | $C_{18}H_{21}N_4SOCl$ | — |
| VIc | 210 | 55 | $C_{18}H_{21}N_4SOCl$ | — |

*Contd*

Table 1—Characterization Data of Compounds IIc,e, IIIc,e, IVc,e, Ve and VIc,e—(*Contd.*)

| Compd ($R_1$ or Ar) | m.p. (°C) | Yield (%) | Mol. formula* | PMR ($\delta$ scale) |
|---|---|---|---|---|
| (Ar = *p*-$ClC_6H_4$) | | | | |
| VIc (Ar = *p*-$Me_2NC_6H_4$) | 125 | 48 | $C_{20}H_{27}N_5SO$ | — |
| VIe (Ar = 3,4-$(MeO)_2C_6H_3$) | 185 | 31 | $C_{19}H_{24}N_4O_3S$ | — |
| VIe (Ar = *o*-$ClC_6H_4$) | 255 | 44 | $C_{17}H_{19}N_4OSCl$ | — |
| VIe (Ar = *m*-$ClC_6H_4$) | 240 | 55 | $C_{17}H_{19}N_4OSCl$ | — |
| VIe (Ar = $C_6H_5$) | 185 | 61 | $C_{17}H_{20}N_4OS$ | — |

*All the compounds gave satisfactory S analysis.

*7′-(m,p-Dimethoxybenzylidene)-6′(7′H)-oxospiro[cyclooctane-1,3′(4′H)-[2H]thiazolo[3,2-b]-s-tetrazine] (VIc, Ar = 3,4(MeO)$_2$C$_6$H$_3$)*

This was synthesized by two methods.

Method-a: A mixture of IIIc (0.635 g, 0.0025 mol), 3,4-dimethoxybenzaldehyde (0.42 g, 0.0025 mol), anhydrous sodium acetate (0.21 g, 0.0025 mol) in gl. acetic acid (10 ml) was heated, under reflux, for 3 hr. The reaction mixture was kept overnight and the yellow solid, thus obtained, was filtered, washed well with water and crystallized from gl. acetic acid to give VIc (Ar = 3,4(MeO)$_2$C$_6$H$_3$) as yellow needles.

Method-b: A mixture of IIc (0.53 g, 0.0025 mol), ethyl chloroacetate (0.31 g, 0.0025 mol), pyridine (0.25 mol) and anhydrous ethanol (10 ml) was heated, under reflux, on a steam-bath for 4 hr. 3,4-Dimethoxybenzaldehyde (0.42 g, 0.0025 mol) and piperidine (0.18 mol) were added and the reaction mixture was refluxed further for 3 hr, kept overnight at room temperature and the yellow solid, thus obtained, was filtered, washed well with water and crystallized from gl. acetic acid to furnish VIc (Ar = 3,4(MeO)$_2$C$_6$H$_3$) as yellow needles, yield 0.6 g (60%), m.p. remained undepressed on admixture with VIc (Ar = 3,4(MeO)$_2$C$_6$H$_3$) obtained by method (a).

The characterization data of VIc,e prepared by the method (a) are given in Table 1.

**Acknowledgement**

SN and VB are thankful to the CSIR, New Delhi and BRS to the UGC, New Delhi for the award of junior research fellowships; GD thanks the UGC for the award of teacher-fellowship and Govt of Haryana for the grant of study leave; KKJ thanks the UGC for the award of teacher-fellowship and authorities of GMN College, Ambala Cantt for grant of study leave; and RD thanks the authorities of Kurukshetra University for facilities.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 744-747

# Pyrroloquinolines: Part IV†—Synthesis of 1-Aryl-1*H*-pyrrolo[2, 3-*b*]quinolines

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*Received* 1 *August* 1986; *revised and accepted* 2 *January* 1987

A wide variety of 1-aryl-2-chloro-1*H*-pyrrolo[2, 3-*b*]quinolines (**3**) have been synthesised by cyclocondensation of 2-quinolone-3-acetanilides (**2**) with phosphoryl chloride. The chloropyrroloquinolines on hydrogenolysis afford the corresponding pyrroloquinolines (**5**) or their dihydroderivatives (**6**) or a mixture of both.

It was demonstrated earlier[2] by Shanmugam and co-workers that 2-quinolone-3-acetanilides (**2**) readily undergo cyclo-condensation with phosphoryl chloride to yield 1-aryl-2-chloro-1*H*-pyrrolo-[2, 3-*b*]quinolines (**3**). The neat entry, thus gained into the titled pyrroloquinoline system, was since then tested with a wide variety of 2-quinolone-3-acetanilides and this article gives an account of them and also the hydrogenolysis experiments carried on **3** which lead to **5** or **6** or both. The interest in the pyrrolo[2, 3-*b*]quinoline system stems from its antiinflammatory, antibacterial, antihypertensive, antipyretic and anticonvulsant properties, and interferon inducing activity as reported in the literature[3]. Further, this paper also reports on a simple technique for obtaining the anilides (**2**) from the quinolone-3-acetic acids (**1**).

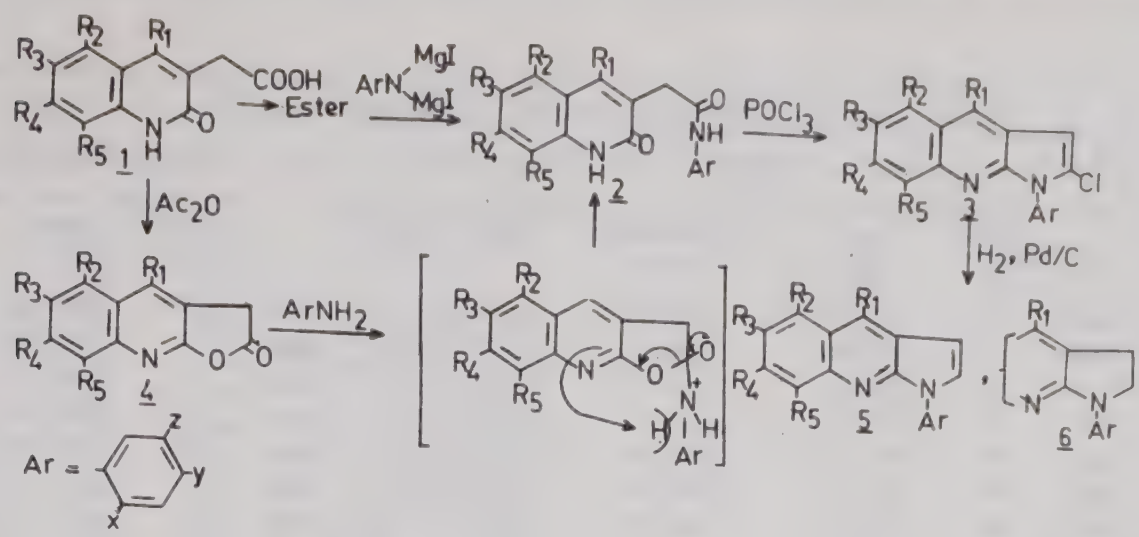
In the procedure formerly[2] employed for obtaining the anilide, the quinolone acid was converted into its ester and then reacted with bis(iodomagnesium)aniline according to the method of Reid and Kahr[4]. But, scrupulously anhydrous conditions have to be maintained during the preparation of the reagent as well as its reaction with the ester. Further, it is apprehended that in a reaction employing this Grignard-type reagent, nuclear halogen may not be tolerated. As an alternative way of arriving at the anilide (**2**) we heated **1a** with acetic anhydride to give the lactone **4a**[5] (Scheme 1) which, when heated with aniline in boiling benzene solution, readily furnished the anilide **2a** in a good yield. Extension of this simple technique to a varied combination of anilines and lactones (**4**; Table 1) provided, in good yields, the corresponding anilides (**2**; Scheme 1) as summarised in Table 2. Availability of the quinolone acids in several varieties particularly through the novel one-step preparation[6] from aconanilides rendered the above route to the titled system more expedient and widely applicable. In many cases, it was rather difficult to obtain the lactone in an analytically pure state. In these cases, the crude lactone obtained after removal of the unused acetic anhydride *in vacuo* was mixed with aniline in benzene solution and heated, as a one-pot reaction, to furnish the anilide. Addition of a few drops of gl. acetic acid to the reaction mixture containing the lactone and the aniline was found to improve the yield of the anilide considerably. The anilides, thus obtained, were converted into the corresponding 1-aryl-2-chloro-pyrroloquinolines (**3**) by heating with phosphoryl chloride according to the procedure report-

Table 1—Lactones of Quinolone-3-acetic Acids (**4**)

| Lactone* | Yield (%) | m.p. °C | Mol. formula |
|---|---|---|---|
| **4a** | 87 | 206-208 (Acetone) | $C_{12}H_9NO_2$ |
| **4b** | 88 | 182-184 (Acetone) | $C_{11}H_7NO_2$ |
| **4c** | 84 | 215-217 | $C_{12}H_9NO_2$ |
| **4d** | 82 | — | — |
| **4e** | 88 | 193-194 (Acetone) | $C_{12}H_9NO_3$ |
| **4f** | 87 | — | — |
| **4g** | 79 | 200-201 (Acetone) | $C_{11}H_6NO_2Cl$ |
| **4h** | 90 | 198-199 (Benzene) | $C_{17}H_{11}NO_2$ |
| **4i** | 85 | 195-196 (Benzene) | $C_{18}H_{13}NO_2$ |
| **4j** | 84 | 256-258 (Benzene) | $C_{17}H_{10}NO_2Cl$ |
| **4k** | 77 | 187-188 (Acetone) | $C_{18}H_{13}NO_2$ |
| **4l** | 79 | — | — |
| **4m** | 71 | — | — |

*$\nu C=O$ around 1820 $cm^{-1}$.

†For part III of the series, see ref. 1.

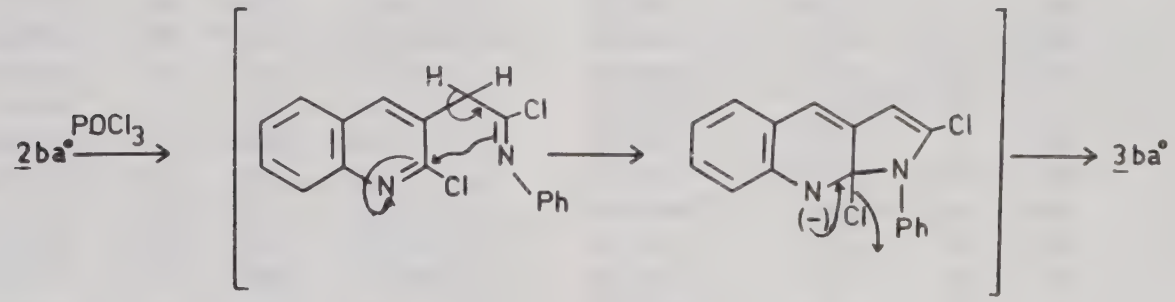


a°) X=Y=Z=H
b°) X=Z=H, Y=$CH_3$
c°) X=$CH_3$, Y=Z=H
d°) X=Z=H, Y=$OCH_3$
e°) X=Z=$OCH_3$, Y=H
f°) X=Z=H, Y=Cl
g°) X=Cl, Y=Z=H
h°) X=Z=H, Y=Br

a) $R_1$=$CH_3$, $R_2$=$R_3$=$R_4$=$R_5$=H
c) $R_1$=$R_2$=$R_4$=$R_5$=H, $R_3$=$CH_3$
e) $R_1$=$R_2$=$R_4$=$R_5$=H, $R_3$=$OCH_3$
g) $R_1$=$R_2$=$R_4$=$R_5$=H, $R_3$=Cl
i) $R_1$=$C_6H_5$, $R_2$=$R_4$=$R_5$=H, $R_3$=$CH_3$
k) $R_1$=$C_6H_4$-$CH_3$(P), $R_2$=$R_3$=$R_4$=$R_5$=H
m) $R_1$=$C_6H_3(CH_3)_2$(2,5), $R_2$=$R_3$=$R_4$=$R_5$=H

b) $R_1$=$R_2$=$R_3$=$R_4$=$R_5$=H
d) $R_1$=$R_2$=$R_3$=$R_4$=H, $R_5$=$CH_3$
f) $R_1$=$R_3$=$R_4$=H, $R_2$=$R_5$=$OCH_3$
h) $R_1$=$C_6H_5$, $R_2$=$R_3$=$R_4$=$R_5$=H
j) $R_1$=$C_6H_5$, $R_2$=$R_4$=$R_5$=H, $R_3$=Cl
l) $R_1$=$C_6H_4$-$OCH_3$(P), $R_2$=$R_3$=$R_4$=$R_5$=H

Scheme 1



Scheme 2

ed earlier[2]. The results are summarised in Table 2. The conversion can be mechanistically viewed as illustrated in the case of **2ba°** (Scheme 2).

Having obtained 1-aryl-2-chloropyrrolo[2,3-*b*]quinolines (**3**), we sought to remove the chlorine atom at $C_2$-position with a view to deriving the corresponding pyrroloquinolines (**5**). Recently[7], a review has appeared on the catalytic methods that have proved effective in the hydrogenolysis of organic halides particularly heteroaryl halides. In connection with our work on benzo[*k*]phenanthridines, we have dechlorinated[8] several 6-chlorobenzo[*k*]phenanthridines by hydrogenolysis using Pd/C in ethanol containing traces of potassium hydroxide. Expecting a similar outcome, we subjected (i) **3aa°**, (ii) **3ac°**, (iii) **3ag°**, (iv) **3ha°**, (v) **3ka°**, (vi) **3kb°**, (vii) **3kc°**, (viii) **3kd°**, (ix) **3ba°**, (x) **3bb°**, (xi) **3bd°**, (xii) **3cb°**, (xiii) **3cd°**, and (xiv) **3ed°** to hydrogenolysis using 5% Pd/C under the same conditions. The results are summarised in Table 3. It was found that the $C_4$-unsubstituted chloropyrroloquinolines (ix-xiv) gave, in addition to the corresponding dechlorinated compounds, the dihydropyrroloquinolines **6ba°**, **6bb°**, **6bd°**, **6cb°**, **6cd°**, **6ed°** respectively. In the case of **3ag°** the chlorine in the 1-phenyl group also underwent hydrogenolysis as shown by the identity of the product with **5aa°**, derived from **3aa°**. Interestingly, when 10% Pd/C was used the $C_4$-substituted chloropyrroloquinolines gave the same products as with 5% Pd/C, whereas the $C_4$-unsubstituted ones yielded the corresponding dihydropyrroloquinolines exclusively.

## Experimental Procedure

Melting points were determined on a Boetius Micro heating table and are uncorrected. IR spectra were recorded on a Perkin-Elmer 597 spectrophotometer, and PMR spectra on a Varian EM-390 (90 MHz) or a Hitachi-FT-R-600 spectrometer using tetramethylsilane as internal reference.

### 2-*Quinolone*-3-*acetic acid* (**1m**)

The acid **1m** was prepared from 2-amino-2′, 5′-dimethylbenzophenone[12] according to the general procedure reported earlier[9].

Table 2—1-Aryl-2-chloropyrrolo[2, 3-*b*]quinolines (**3**)

| Starting lactone | Ar of aniline used | Anilides* | | | | | Chloropyrroloquinolines† | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Yield (%) | m.p. °C | Recrystallized from | Mol. formula† | | Yield (%) | m.p. °C | Mol. formula† |
| **4a** | a° | **2aa°** | 85 | 316-17 | MeOH | $C_{18}H_{16}N_2O_2$ | **3aa°** | 67 | 153-54 | $C_{18}H_{13}N_2Cl$ |
| | b° | **2ab°** | 85 | 294-96 | MeOH | $C_{19}H_{18}N_2O_2$ | **3ab°** | 67 | 149-50 | $C_{19}H_{15}N_2Cl$ |
| | c° | **2ac°** | 91 | 282-83 | EtOH | $C_{19}H_{18}N_2O_2$ | **3ac°** | 72 | 115-17 | $C_{19}H_{15}N_2Cl$ |
| | d° | **2ad°** | 90 | 305-6 | MeOH | $C_{19}H_{18}N_2O_3$ | **3ad°** | 62 | 178-79 | $C_{19}H_{15}N_2OCl$ |
| | e° | **2ae°** | 79 | 264-65 | MeOH | $C_{20}H_{20}N_2O_4$ | **3ae°** | 69 | 196-97 | $C_{20}H_{17}N_2O_2Cl$ |
| | f° | **2af°** | 84 | 283-84 | MeOH | $C_{18}H_{15}N_2O_2Cl$ | **3af°** | 50 | 177-78 | $C_{18}H_{12}N_2Cl_2$ |
| | g° | **2ag°** | 88 | 280-82 | EtOH | $C_{18}H_{15}N_2O_2Cl$. | **3ag°** | 70 | 151-52 | $C_{18}H_{12}N_2Cl_2$ |
| | h° | **2ah°** | 70 | 280-82 | MeOH | $C_{18}H_{15}N_2O_2Br$ | **3ah°** | 52 | 170-72 | $C_{18}H_{12}N_2Cl_2$ |
| **4b** | a° | **2ba°** | 77 | 228-30 | MeOH | $C_{17}H_{14}N_2O_2$ | **3ba°** | 60 | 145-47 | $C_{17}H_{11}N_2Cl$ |
| | b° | **2bb°** | 83 | 256-57 | MeOH | $C_{18}H_{16}N_2O_2$ | **3bb°** | 65 | 128-29 | $C_{18}H_{13}N_2Cl$ |
| | d° | **2bd°** | 85 | 245-46 | MeOH | $C_{18}H_{16}N_2O_3$ | **3bd°** | 67 | 161-62 | $C_{18}H_{13}N_2OCl$ |
| | f° | **2bf°** | 87 | 267-68 | MeOH | $C_{17}H_{13}N_2O_2Cl$ | **3bf°** | 68 | 190-92 | $C_{17}H_{10}N_2Cl_2$ |
| **4c** | b° | **2cb°** | 72 | 274-76 | DMF-MeOH | $C_{19}H_{18}N_2O_2$ | **3cd°** | 60 | 172-73 | $C_{19}H_{15}N_2Cl$ |
| | d° | **2cd°** | 77 | 261-62 | EtOH | $C_{19}H_{18}N_2O_3$ | **3cd°** | 50 | 166-67 | $C_{19}H_{15}N_2OCl$ |
| | f° | **2cf°** | 79 | 280-81 | MeOH | $C_{18}H_{15}N_2O_2Cl$ | **3cf°** | 58 | 220-21 | $C_{18}H_{12}N_2Cl_2$ |
| | h° | **2ch°** | 75 | 282-83 | MeOH | $C_{18}H_{15}N_2O_2Br$ | **3ch°** | 58 | 165-67 | $C_{18}H_{12}N_2ClBr$ |
| **4d** | b° | **2db°** | 81 | 263-64 | $CHCl_3$ | $C_{19}H_{18}N_2O_2$ | **3db°** | 65 | 113-14 | $C_{19}H_{15}N_2Cl$ |
| **4e** | d° | **2ed°** | 72 | 268-69 | MeOH | $C_{19}H_{18}N_2O_4$ | **3ed°** | 50 | 162-64 | $C_{19}H_{15}N_2O_2Cl$ |
| **4f** | f° | **2ff°** | 78 | 273-74 | MeOH | $C_{19}H_{17}N_2O_4Cl$ | **3ff°** | 58 | 223-24 | $C_{19}H_{14}N_2O_2Cl_2$ |
| **4g** | b° | **2gb°** | 73 | 202-03 | MeOH | $C_{18}H_{15}N_2O_2Cl$ | **3gb°** | 49 | 202-3 | $C_{18}H_{12}N_2Cl_2$ |
| **4h** | a° | **2ha°** | 79 | 282-83 | MeOH | $C_{23}H_{18}N_2O_2$ | **3ha°** | 60 | 192°(d) | $C_{23}H_{15}N_2Cl$ |
| | b° | **2hb°** | 80 | 275-76 | MeOH | $C_{24}H_{20}N_2O_2$ | **3hb°** | 59 | 179°(d) | $C_{24}H_{17}N_2Cl$ |
| | f° | **2hf°** | 81 | > 310 | MeOH | $C_{23}H_{17}N_2O_2Cl$ | **3hf°** | 63 | 196 (d) | $C_{23}H_{14}N_2Cl_2$ |
| **4i** | a° | **2ia°** | 82 | 250-52 | MeOH | $C_{24}H_{20}N_2O_2$ | **3ia°** | 53 | 188-89 | $C_{24}H_{17}N_2Cl$ |
| **4j** | b° | **2jb°** | 81 | > 300 | MeOH | $C_{24}H_{19}O_2Cl$ | **3jb°** | 58 | 230-32 | $C_{24}H_{16}N_2Cl_2$ |
| | d° | **2jd°** | 79 | > 300 | MeOH | $C_{24}H_{19}N_2O_3Cl$ | **3jd°** | 60 | 264-65 | $C_{24}H_{16}N_2OCl_2$ |
| **4k** | a° | **2ka°** | 82 | 320-21 | DMF-$H_2O$ | $C_{24}H_{20}N_2O_2$ | **3ka°** | 70 | 186-87 | $C_{24}H_{17}N_2Cl$ |
| | b° | **2kb°** | 79 | > 315 | MeOH | $C_{25}H_{22}N_2O_3$ | **3kb°** | 67 | 186-87 | $C_{25}H_{19}N_2Cl$ |
| | c° | **2kc°** | 80 | 283-85 | MeOH | $C_{25}N_{22}N_2O_2$ | **3kc°** | 71 | 143-44 | $C_{25}H_{19}N_2Cl$ |
| | d° | **2kd°** | 80 | 262-63 | MeOH | $C_{25}H_{22}N_2O_3$ | **3kd°** | 67 | 199-200 | $C_{25}H_{19}N_2OCl$ |
| **4l** | b° | **2lb°** | 79 | 236-38 | MeOH | $C_{25}H_{22}N_2O_3$ | **3lb°** | 52 | 186-88 | $C_{25}H_{19}N_2OCl$ |
| **4m** | d° | **2md°** | — | — | — | — | **3md°** | 50 | 176-80 | $C_{26}H_{21}N_2OCl$ |

*$\nu$NH around 3280 and $\nu$C = O (amide) at 1630-1680; in the case of **2cf°**, **2ed°**, **2ff°** and **2ka°** an additional amide band appeared at 1670 $cm^{-1}$.

†All the compounds gave satisfactory elemental analyses (C ±0.45% and H ±0.40% within the theoretical values).

‡Recrystallized from benzene petrol.

*Preparation of the lactones* (**4**): *General procedure*

A mixture of the quinolone acid (**1**, 0.01 mol) and acetic anhydride (0.06 mol) was heated in an oil-bath at 100-105°C for 4 hr, the excess acetic anhydride stripped off under vacuum and the residue gently stirred with ice water and filtered. The precipitate was collected, washed with ice cold sodium bicarbonate solution, filtered, dried and recrystallised from a suitable solvent. This technique was tried with the following acids: **1a**[5,11], **1b**[6a], **1c**[6a], **1d**[6a], **1e**[6b], **1f**[6b], **1g**[6b], **1h**[9], **1i**[9], **1j**[9], **1k**[10], **1l**[10], and **1m**. The lactones from the acids **1d**, **1f**, **1l** and **1m** were not obtainable in an analytically pure state. Therefore, these lactones were used in the next stage without further purification (for yield, m.p., etc of **4** see Table 1).

*Reaction of* **4** *with anilines: General procedure*

To a mixture of **4** (0.001 mol ) and an appropriate aniline (0.025 mol) in benzene (150 ml), a few drops (3-4) of gl. acetic acid were added and the reaction mixture was refluxed on a steam-bath for 4 hr. The solvent was distilled off and the residue digested with 2*N* HCl (35 ml), filtered, washed with 10 ml of ice cold 2% aq. sodium hydroxide, then with water, dried and recrystallised from a suitable solvent (for yield, m.p., etc of **2** see Table 2).

The anilides (**2**) were then cyclized with $POCl_3$ and the products worked-up according to the procedure reported earlier[2] to give the chloropyrroloquinoline (**3**). The PMR spectrum of **3aa°** in $CDCl_3$ exhibited signals at $\delta$ 2.87 (*s*, 3H, $CH_3$), 6.73

Table 3—Products of Hydrogenolysis of 1-Aryl-2-chloropyrrolo[2, 3-*b*]quinolines (**3**): Formation of **A** [Pyrroloquinolines (**5**)] + **B** [dihydropyrroloquinolines (**6**)]

| Substrate | A* | Yield (%) (Pd/C 5%) | Yield (%) (Pd/C 10%) | m.p. °C | Mol. formula† | B‡ | Yield (%) (Pd/C 5%) | Yield (%) (Pd/C 10%) | m.p. °C | Mol. formula† |
|---|---|---|---|---|---|---|---|---|---|---|
| **3aa°** | **5aa°** | 74 | 81 | 95-97 | $C_{18}H_{14}N_2$ | — | — | — | — | — |
| **3ac°** | **5ac°** | 67 | 69 | 85-86 | $C_{19}H_{16}N_2$ | — | — | — | — | — |
| **3ha°** | **5ha°** | 72 | 71 | 116-17 | $C_{23}H_{16}N_2$ | — | — | — | — | — |
| **3ka°** | **5ka°** | 77 | 79 | 127-28 | $C_{24}H_{18}N_2$ | — | — | — | — | — |
| **3kb°** | **5kb°** | 82 | 85 | 148-50 | $C_{25}H_{20}N_2$ | — | — | — | — | — |
| **3kc°** | **5kc°** | 77 | 87 | 95-96 | $C_{25}H_{20}N_2$ | — | — | — | — | — |
| **3kd°** | **5kd°** | 85 | 86 | 161-62 | $C_{25}H_{20}N_2O$ | — | — | — | — | — |
| **3ag°** | **5aa°** | 68 | 69 | 95-96 | $C_{18}H_{14}N_2$ | — | — | — | — | — |
| **3ba°** | **5ba°** | 51 | — | 61-62 | $C_{17}H_{12}N_2$ | **6ba°** | 28 | 85 | 165 (d) | $C_{17}H_{14}N_2$ |
| **3bb°** | **5bb°** | 57 | — | 74-75 | $C_{18}H_{14}N_2$ | **6bb°** | 22 | 90 | 148-49 | $C_{18}H_{16}N_2$ |
| **3bd°** | 5bd° | 51 | — | 66-67 | $C_{18}H_{14}N_2O$ | **6bd°** | 28 | 95 | 144-45 | $C_{19}H_{16}N_2O$ |
| **3cb°** | **5cb°** | 56 | — | 94-96 | $C_{19}H_{16}N_2$ | **6cb°** | 22 | 84 | 168-69 | $C_{19}H_{18}N_2$ |
| **3cd°** | 5cd° | 67 | — | 113-14 | $C_{19}H_{16}N_2O$ | **6cd°** | 17 | 89 | 142-43 | $C_{19}H_{18}N_2$ |
| **3ed°** | **5ed°** | 45 | — | 95-96 | $C_{19}H_{16}N_2O_2$ | **6ed°** | 22 | 77 | 139-40 | $C_{19}H_{18}N_2N_2O_2$ |

*Recrystallized from petrol (40-60°)
†All the products gave satisfactory elemental analyses (C ±0.50% and H ±0.40% within the theoretical values)
‡Recrystallized from petrol (60-80°)

(*s*, 1H, $C_3$-H), 7.10-8.20 (*m*, 9H, Ar-*H*) (for yield, m.p., etc of **3** see Table 2).

*Hydrogenolysis of* 1-*aryl*-2-*chloropyrrolo*-[2,3-*b*]*quinolines* (**3**): *General procedure*

To a solution of **3** (100 mg) in 95% ethanol (100 ml) were added Pd/C (500 mg) and a pellet of KOH and the mixture was shaken with hydrogen at 20-30 psi for 1 hr in a Cook's low pressure hydrogenator. Thereafter, the catalyst was filtered off and the solvent evaporated to furnish a residue which on column chromatography over silica gel using petrol-benzene (2 : 1) as eluant gave the product. It recrystallised from a suitable solvent. The PMR spectrum of **5aa°** in $CDCl_3$ exhibited signals at $\delta$ 2.92 (*s*, 3H, $CH_3$), 6.71 (*d*, 1H, $J$ = 3.6 Hz, $C_3$-H), 7.23-8.23 (*m*, 10H, Ar-*H*) (for yield, m.p. etc of the products see Table 3).

**Acknowledgement**

One of the authors (SS) thanks the Management of Sri Avinashilingam Home Science College for Women, Coimbatore for a research fellowship. A grant for the purchase of Hitachi F T NMR R 600 spectrometer by the Department of Science and Technology is gratefully acknowledged. The authors also thank Dr S Rajappa of CIBA Research Centre, Bombay and Dr B R Pai of R&D of Amrutanjan Ltd., for elemental analyses and PMR spectra of some of the compounds.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 748-751

# Studies in Potential Filaricides: Part 19—Synthesis of 1-Methyl-4-substitutedcarbonylpiperazines as Diethylcarbamazine Analogs†

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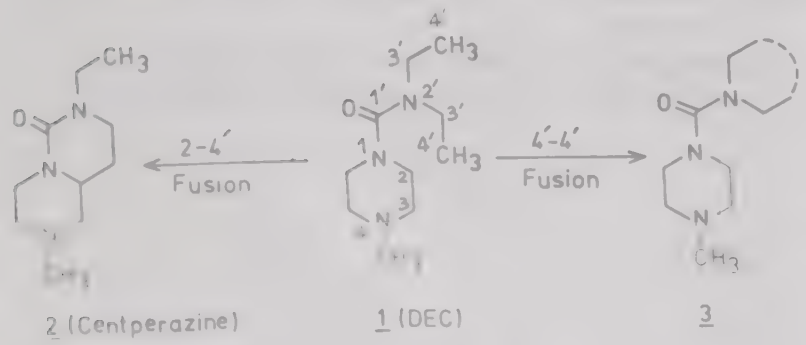
*Received* 15 *January* 1987; *accepted* 20 *February* 1987

The synthesis and antifilarial activity of a series of 1-methyl-4-substitutedcarbamoyl- and carbonylpiperazines (**6-42**) against *Litomosoides carinii* in cotton rats and *Dipetalonema viteae* in *Mastomys natalensis* are described. The most potent compound of this series, 1-methyl-4-(pyrrolidin-1-yl)carbonylpiperazine (**7**) causes 95-98% reduction of blood microfilarial count in cotton rats infected with *L. carinii* at an intraperitoneal or oral dose of 1.5 (base) or 3 (citrate) mg/kg given for 6 days. A number of other compounds also exhibit marked microfilaricidal effect in the dose range of 6-30 mg/kg.

Diethylcarbamazine (DEC, **1**), despite its shortcomings, is still used as the drug of choice for treating or suppressing various forms of human filariases[10]. Attempts to improve the biological profile of DEC have led to the syntheses of a wide variety of structural analogs; however no ideal antifilarial has yet emerged[2]. Recently 3-ethyl-8-methyl-1, 3, 8-triazabicyclo[4.4.0]decan-2-one (**2**), a bicyclic analog of DEC with 'frozen conformation' was synthesized in this laboratory and it showed microfilaricidal activity superior to DEC[3-5]. Compound (**2**) represents DEC with greatly reduced conformational mobility of the diethylcarbamoyl side chain; however one of the ethyl groups still has rotational freedom. In an effort to further improve the antifilarial activity of this class of compounds we became interested in synthesizing 1-methyl-4-substitutedcarbonyl piperazines (**3**) which would resemble DEC, except that the free rotation of both the ethyl groups would be restricted by incorporation into a cyclic structure.

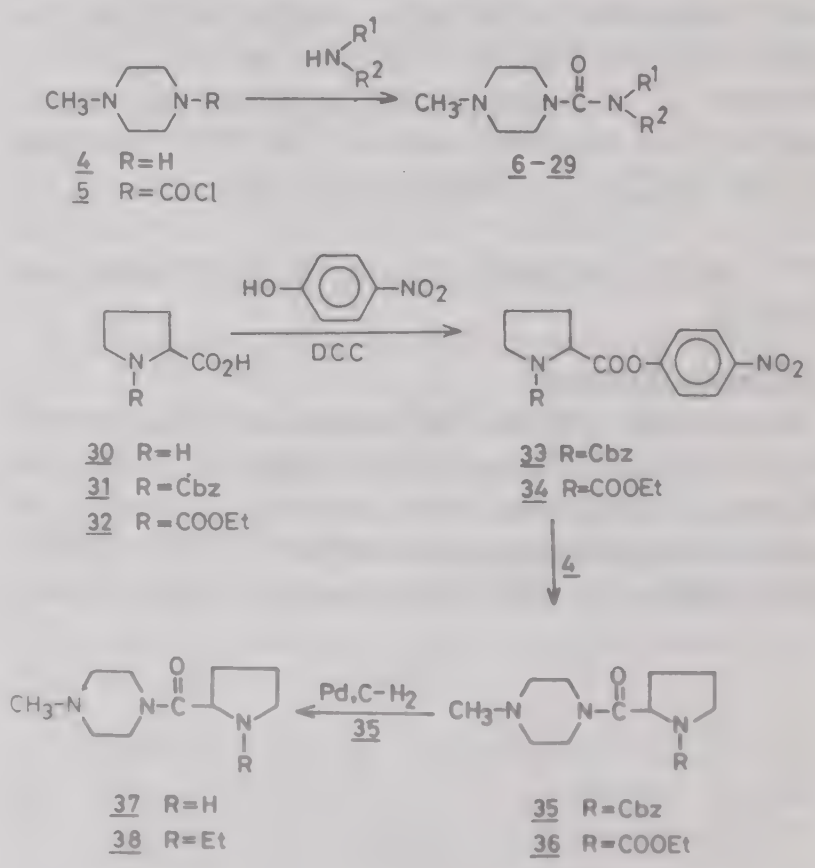
The present communication describes the synthesis and filaricidal activity of various 1-methyl-4-substitutedcarbonyl-piperazines (**6-29**) (Scheme 1). Since 1-methyl-4-(pyrrolidin-1-yl)carbonyl-piperazine (**7**) showed improved filaricidal activity compared to DEC, some of its structural analogs (**35-38**) were also prepared.




2 (Centperazine) 1 (DEC) 3

## *Chemistry*

Treatment of a solution of 1-methylpiperazine (**4**) with phosgene yielded 1-methyl-4-chlorocarbonyl-piperazine (**5**)[6] which was condensed with different amines in the presence of triethylamine to afford




Scheme 1

† CDRI Communication No. 3841

1-methyl-4-substitutedcarbonyl-piperazines (**6-29**) (Table 1).

1-Benzyloxycarbonylproline (**31**)[7] and 1-carbethoxyproline (**32**), obtained by condensation of proline (**30**) with benzyloxycarbonyl chloride and ethyl chloroformate respectively, on reaction with 4-nitrophenol in the presence of DCC yielded the corresponding 4-nitrophenyl esters **33** and **34**. Treatment of **33** and **34** with **4** at room temperature furnished 1-methyl-4-(1-benzyloxycarbonylpyrrolidin-2-carbonyl)piperazine (**35**) and 1-methyl-4-(1-carbethoxypyrrolidin-2-carbonyl)piperazine (**36**) in ex-

Table 1—Chemical and Biological Data of Compounds **6-29**

| Compd | N $R^1$ | Mol. formula | Yield % | m.p./b.p. °C | Dose mg/kg×6 (i.p.) | Antifilarial activity | |
|---|---|---|---|---|---|---|---|
| | | | | | | %Reduction of microfilarial counts on day[7] | Remarks |
| **6** | Aziridin-1-yl | $C_8H_{15}N_3$ | 81 | oil[b] | 30 | Nil | Inactive |
| **7** | Pyrrolidin-1-yl | $C_{10}H_{19}N_3O$ | 76 | 130-5/5 mm | 1.5 | 92 | Active, 60% suppression of microfilarial counts upto day 100 |
| | | | | 165(citrate) | 3 | 93 | |
| **8** | Piperidin-1-yl | $C_{11}H_{21}N_3O$ | 80 | oil | 3 | 95 | Active, 40% reduction of microfilariae on day 45 |
| **9** | 2-Methylpiperidin-1-yl | $C_{12}H_{23}N_3O$ | 71 | oil | 3 | 95 | Active, at 30 mg/kg×6, suppresses microfilarial counts upto 35 days |
| **10** | 3-Methylpiperidin-1-yl | $C_{12}H_{23}N_3O.HCl$ | 60 | 138-41 | 3 | 95 | Active |
| **11** | 4-Methylpiperidin-1-yl | $C_{12}H_{23}N_3O$ | 70 | 88-90 | 10 | 70 | |
| | | | | | 30 | 95 | Active |
| **12** | 4-Ethylpiperidin-1-yl | $C_{17}H_{25}N_3O$ | 84 | oil | 30 | 100 | Active, suppresses microfilarial counts upto 42 days. |
| **13** | 4-Phenylpiperidin-1-yl | $C_{17}H_{25}N_3O$ | 60 | oil | 30 | 100 | Active, at 30 mg/kg×6, suppresses microfilarial counts upto 42 days |
| **14** | 4-Hydroxy-4-phenyl piperidin-1-yl | $C_{17}H_{25}N_3O_2$ | 66 | 148-50 | 1 | 80 | Active |
| | | | | | 3 | 95 | |
| **15** | Homopiperidin-1-yl | $C_{12}H_{23}N_3O$ | 73 | oil | 10 | 95 | Active, at 30 mg/kg×6, 60% suppression of microfilaraemia upto 42 days. |
| **16** | 4-Phenylpiperazin-1-yl | $C_{17}H_{25}N_3O$ | 65 | 110 | 30 | 95 | do |
| **17** | 4-Carbethoxypiperazin-1-yl | $C_{13}H_{24}N_4O_3$ | 35 | oil | 30 | nil | Inactive |
| **18** | 4-(1-Methylpiperazinyl)carbonylpiperazin-1-yl | $C_{16}H_{30}N_6O_2$ | 50 | 204-6 | 30 | nil | do |
| **19** | 4-(2-Chlorophenyl) piperazin-1-yl | $C_{16}H_{23}ClN_4O$ | 75 | 110 | 30 | nil | do |
| **20** | 4-Methyl-1-amino-piperazinyl | $C_{11}H_{23}N_5O$ | 62 | oil | 30 | nil | do |
| **21** | N-Phenylamino | $C_{12}H_{17}N_3O$ | 54 | oil | 30 | nil | do |
| **22** | Cyclohexylamino | $C_{12}H_{23}N_3O$ | 70 | oil | 30 | nil | do |
| **23** | Hydrazino | $C_6H_{14}N_4O$ | 58 | 135 | 30 | nil | do |
| **24** | Benzylamino | $C_{13}H_{19}N_3O$ | 70 | 128 | 30 | nil | do |
| **25** | N-Benzylmethylamine | $C_{14}H_{21}N_3O$ | 65 | oil | 30 | nil | do |
| **26** | 2-Hydroxyethylamino | $C_8H_{17}N_3O_2$ | 66 | oil | 30 | nil | do |
| **27** | Imidazol-1-yl | $C_9H_{14}N_4O$ | 68 | oil | 30 | nil | do |
| **28** | 2-Methylimidazol-1-yl | $C_{10}H_6N_4O$ | 60 | oil | 30 | 94 | Active, suppresses the release of microfilariae by 50% upto 28 days. |
| **29** | Di-(2-hydroxyethyl)amino | $C_{10}H_{21}N_3O$ | 50 | oil | 30 | nil | do |

(a) All the compounds were analysed for C, H and N and the results were within ±0.5% of the calculated values.

(b) All the compounds, obtained as oil, were purified over a basic alumina column using chloroform/ethylacetate as eluant.

cellent yields. Hydrogenation of **35** in the presence of Pd-C catalyst led to 1-methyl-4-(pyrrolidin-2-carbonyl)piperazine (**37**) which was condensed with ethyl iodide to form 1-methyl-4-(1-ethylpyrrolidin-2-carbonyl)piperazine (**38**) (Scheme 1).

*Biological activity*

The micro- and macro-filaricidal activities of the compounds were tested against the experimental infection of *Litomosoides carinii* in cotton rats (*Sigmondon hispidus*). The filarial infection was transmitted to cotton rats through the vector *Liponyssus bacoti* using the technique of Hawking and Sewell[8]. At the end of prepatent period, animals showing 250 or more microfilariae per 5 µl of blood were used in the experiment. Blood samples of both experimental and control animals were examined before starting the treatment and 3-4 animals were kept as controls. The compounds were dissolved either in water or Tween 80 and then given orally, subcutaneously or intraperitoneally for 6 days at a dose level equivalent to 1/5th of the maximum tolerated dose.

Blood smears of the animals were examined for the presence of microfilariae at weekly intervals upto 6 weeks since the onset of the treatment. On the day 42, all the treated and control group of animals were sacrificed and the condition of the adult male and female filarial worms was observed. The micro- and macrofilarial activities of the compounds were assessed by the method of Lämmler and coworkers[9].

A similar method was followed to evaluate the filaricidal efficacy of the compounds against *Dipetalonema viteae* in *Mastomys natalensis*.

Initially the compounds were administered intraperitoneally or orally at a dose of 30 mg/kg for 6 days. Those showing reduction in microfilaraemia were tested at lower doses of 10, 5, 3 and 1 mg/kg.

The most active compound of this series is 1-methyl-4-(pyrrolidin-1-yl)carbonyl piperazine (**7**) which removed > 95% of the microfilariae of *L.carinii* from the blood on day 7 at a dose of 1.5 mg/kg given intraperitoneally or orally for 6 days. When given as citrate salt, **7** showed a similar spectrum of activity at an oral or intraperitoneal dose of 3 mg/kg × 6 days. In a parallel experiment, a dose of 6, 12 mg/kg of DEC base or citrate respectively given for 6 days eliminated > 90% of microfilariae from the blood of cotton rats. Neither of the compounds, DEC and **7**, exhibited activity against adult filarial worms of *L.carinii* (Table 2).

Compound **7** was also tested for its micro- and macro-filaricidal action against *Dipetalonema viteae* in *Mastomys natalensis*. At a dose of 25 mg/kg × 6, s.c. **7** caused 90-92% suppression of microfilariemia upto day 42 but did not show any effect on adult worms. DEC showed a similar pattern of activity at a dose of 175 mg/kg × 6 s.c. (Table 2).

A number of other 1-methyl-4-substituted-carbonyl piperazines (**8-16** and **28**) also exhibited marked antifilarial activity at doses of 3-30 mg/kg × 6 i.p. which have been recorded in Table 1. Compounds **35-38** prepared as strucutural analogs of **7** were devoid of activity against *L. carinii* in cotton rats at a dose of 30 mg/kg i.p. given for 6 days.

## Experimental Procedure

The structures of all the compounds were checked by IR on Perkin-Elmer 157 or 177 infracord spectrophotometers ( vmax in $cm^{-1}$). PMR spectra were recorded on a Varian A60-D (60 MHz) instrument using TMS as internal reference (chemical shifts in δ ppm). The purity of the compounds was checked by TLC on silica gel G plates and the spots located using iodine vapours. Melting points were taken in sulphuric acid bath and are uncorrected.

*1-Methyl-4-chlorocarbonylpiperazine hydrochloride* (**5**)

A solution of 1-methylpiperazine (**4**, 100 g; 1 mol) in $CHCl_3$ (250 ml) was added dropwise to a cooled (0-5°C) and stirred solution of phosgene (150 g) in $CHCl_3$ (1 litre) during 1 hr. After the addition was

Table 2 – Comparative Filaricidal Efficacy of 7 and DEC

| Parasite (host) | Compound | Dose mg/kg × 6 (route) | % Reduction of microfilariae in the blood on days after treatment | | | Action on adult worms | $LD_{50}$, mg/kg in mice | Therapeutic index |
|---|---|---|---|---|---|---|---|---|
| | | | 7 | 14 | 21 | | | |
| *L.carinii* (cotton rat) | 7 (citrate) | 3 (i.p.) | 93.3 | 76.0 | 56.0 | nil | 800 | 266 |
| | | 3 (oral) | 92.6 | 90.5 | 74.7 | nil | 3750 | 1250 |
| | DEC citrate) | 12 (i.p.) | 95.9 | 59.7 | 37.4 | nil | 425 | 35 |
| | | 12 (oral) | 95.2 | 76.9 | 30.8 | nil | 1000 | 83 |
| *D.viteae* | 7 (base) | 25 (s.c.) | 90.0 | 95.8 | 96.4 | nil | — | — |
| *M. natalensis*) | DEC (base) | 175 (s.c.) | 99.6 | 94.1 | 94.1 | nil | — | — |

over, the reaction mixture was stirred in ice bath for 2 hr and then at room temperature for 2 hr. The separated white solid was filtered, washed with dry benzene or ether and dried, to give 150 g (75.75%) of **5**.HCl, m.p. 230° (lit.[6] m.p. 229°).

1-*Methyl*-4-*substitutedcarbonylpiperazines* (**6-29**)
*General method*

The method is exemplified by the preparation of 1-methyl-4-(pyrrolidin-1-yl)carbonylpiperazine (**7**).

A solution of pyrrolidine (7.1 g, 0.001 mol) in dry MeOH (50 ml) was added dropwise to a stirred and cooled (ice-water) solution of **5** (19.9 g, 0.1 mol) and $Et_3N$ (28 ml, 0.02 mol) in dry benzene (150 ml). After the addtion was over, the reaction mixture was refluxed on a water-bath for 2 hr. Solvent was removed (100 ml) and the separated $Et_3N$. HCl was filtered off. The filtrate was washed with small amount of water, dried ($Na_2SO_4$) and solvent removed to give 14.8 g (75%) of **7** as an oil b.p. 135-40°/5 mm; m.p. (citrate) 165°; IR (neat): 1660 (CO), PMR($CDCl_3$): 3.2-3.5 [*m*, 8H, $(CH_2)_2$-NCON$(CH_2)_2$], 2.22-2.6 [*m*, 7 H, $CH_3-N-(CH_2)_2$], 1.7-2.0 (*m*, 4H, $CH_2—CH_2—CH_2—CH_2$) (Found: C, 60.8; H, 9.5; N, 21.3. $C_{10}H_{19}N_3O$ requires C, 60.9; H, 9.6; N, 21.3%).

Similarly compound **6** and **8-29** were prepared by treating **5** with respective amines (Table 1).

1-*Methyl*-4-(1-*benzyloxycarbonylpyrrolidin*-2-*yl*)*piperazine* (**35**)

A solution of **33** (7.4 g, 0.02 mol) and **4** (2 g, 0.02 mol) in dry benzene (50 ml) was stirred at room temperature for 6 hr and treated with 1 *N*HCl (50 ml). The aqueous layer was separated and basified to *p*H 8-9 by adding aq NaOH. The resulting solution was extracted with EtOAc (3 × 50 ml), combined extracts dried ($Na_2SO_4$) and solvent removed *in vacuo* to get an oil which was triturated with hexane to give 5.6 g (84.5%) of **35**, m.p. 82°; IR (KBr): 1695 (NCOO), 1640 (NCON); PMR ($CDCl_3$): 7.25 (*s*, 5H, $C_6H_5$), 5.5-5.15 (*t*, 2H, $CH_2$Ph), 4.5-4.8 (*m*, 1H, N—CO—CHN), 3.25-3.85 [*m*, 6H, $(CH_2)_2$NCOCH and CH—N—$CH_2$], 1.7-2.6 [*m*, 11H, $CH_3$—N—$(CH_2)_2$ and —$CH_2$—$CH_2$] (Found: C, 65.7; H, 7.6; N, 12.4. $C_{18}H_{25}N_3O_3$ requires C, 65.3; H, 7.6; N, 12.7%).

1-*Methyl*-4-(1-*carbethoxypyrrolidin*-2-*carbonyl*)*piperazine* (**36**)

This was prepared as an oil in 80% yield by treating **34** with **4** as described above and purified over a basic alumina column using $CHCl_3$ as eluant; IR(neat): 1690 (NCOO), 1650 (NCON); PMR($CCl_4$): 4.3-4.6 (*m*, 1H, NCOC*H*N), 3.95 (*q*, 2H, $OCH_2$—$CH_3$, $J$ = 7Hz), 3.1-3.7 [*m*, 6H, $(CH_2)_2$N—COCH—N$CH_2$], 2.1-2.5 (*m*, 7H, $CH_3$—N—$(CH_2)_2$], 1.65-2.0 (*m*, 4H, C—$CH_2$—$CH_2$—C), 1.2 (*t*, 3H, $OCH_2$—$CH_3$, $J$ = 7 Hz) (Found: C, 37.8; H, 8.7; N, 15.4. $C_{13}H_{23}N_3O_3$ requires C, 58.0; H, 8.5; N, 15.6%).

1-*Methyl*-4-(*pyrrolidin*-2-*carbonyl*)*piperazine* (**37**)

Hydrogen was bubbled through a suspension of **35** (6.62 g, 0.02 mol) and 5% Pd-C (0.6 g) in MeOH (100 ml) until there was no more evolution of $CO_2$ (8 hr). The catalyst was removed by filtration and the filtrate concentrated *in vacuo* to give **37** as an oil which was purified on a silica gel column using $CHCl_3$—MeOH (98:2) as eluant to give 3.2 g (80%) of the product; IR (neat): 3390-3480 (NH), 1650 (CO); PMR($CDCl_3$): 4.62 (*s*, 1H, NH), 3.82-4.06 (*m*, 1H, CO—C*H*—NH), 3.26-3.6 [*m*, 4H, $(CH_2)_2$N—CO], 2.1-2.45 [*m*, 9H, $CH_3$—N—$(CH_2)_2$, NH—$CH_2$], 1.5-2.0 (*m*, 4H, C—$CH_2$—$CH_2$—C) (Found: C, 60.6; H, 9.4; N, 21.0. $C_{10}H_{19}N_3O$ requires C, 60.9; H, 9.6; N, 21.3%).

1-*Methyl*-4-(1-*ethylpyrrolidin*-2-*carbonyl*)*piperazine* (**38**)

A solution of **37** (1.5 g, 0.0075 mol), EtBr (0.9 g, 0.008 mol) and $K_2CO_3$ (0.65 g, 0.005 mol) in dry acetone (30 ml) was stirred at room temperature for 12 hr. The inorganic matter was removed by filtration and the filtrate was concentrated *in vacuo* to give **38** as an oil which was purified on a basic alumina column using EtOAc as eluant to give 1.1 g (60%) of the product; IR (neat): 1630 (CON). PMR($CCl_4$): 3.3-3.8 [*m*, 4H, CON—$(CH_2)_2$], 2.9-3.2 (*m*, 1H, CO—CH—N), 2.1-2.6 [*m*, 11H, $CH_3$—$CH_2$—N—$CH_2$, $CH_3-(CH_2)_2$], 1.6-2.0 (*m*, 4H, C-$CH_2$-$CH_2$-C), 1.0 (*t*, 3H, $CH_2-CH_3$, $J$ = 7 Hz) (Found: C, 64.1; H, 10.4; N, 10.4. $C_{12}H_{23}N_3O$ requires C, 64.0; H, 10.2; N, 18.7%).

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 752-756

# Studies in Potential Filaricides: Part 20—Synthesis of 1,4-Disubstituted Piperazines as Diethylcarbamazine Analogs†

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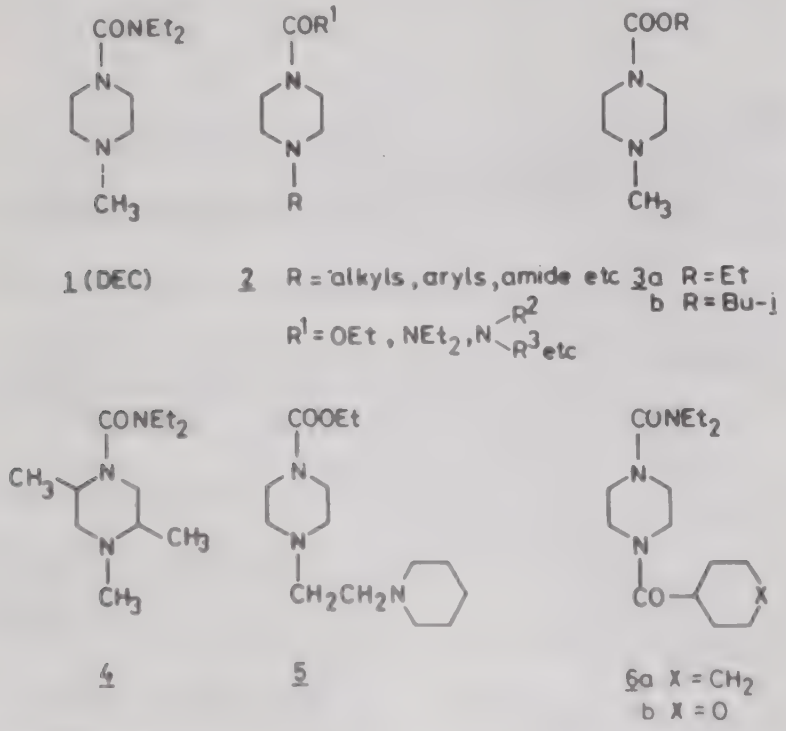
*Received* 14 *April* 1986; *revised and accepted* 13 *October* 1986

A series of substituted 2,4-dimethylpiperazines (**10-15**), 1-benzyl-2-methylpiperazines (**16-19**), 1-substituted 3-methylpiperazines (**20-25**, **27**) and 1,4-disubstituted piperazines (**28-34**) have been synthesized starting from 1-benzyl-2-methylpiperazine (**9**) and 1-(chloroacetyl)-4-methylpiperazine (**28**). The compounds have been tested for their antifilarial activity against *Litomosoides carinii* in cotton rats, but none of them causes reduction in blood microfilarial counts up to a dose of 30 mg/kg i.p. given for 6 days.

Since the discovery of diethylcarbamazine (DEC, **1**) as a drug of choice for the treatment of different forms of human filariasis, a number of its structural congeners have been prepared to improve the therapeutic spectrum of this drug[1,2]. The most rewarding approach to prepare a better analog of DEC had been the synthesis of 1,4-disubstituted piperazines among which **2-6** were found to possess marked microfilarial activity[1,3]. During our efforts to develop ideal filaricides[2,3], it seemed rational to prepare some 1,4-disubstituted piperazines carrying a methyl residue at one of the carbons of the piperazine ring. This would change the geometry of the ring around its vicinal nitrogens and may help in understanding the role of ring conformation in giving rise to antifilarial activity in this class of compounds. The present paper describes the synthesis and antifilarial test results of some 1,4-disubstituted piperazines (**9-34**).

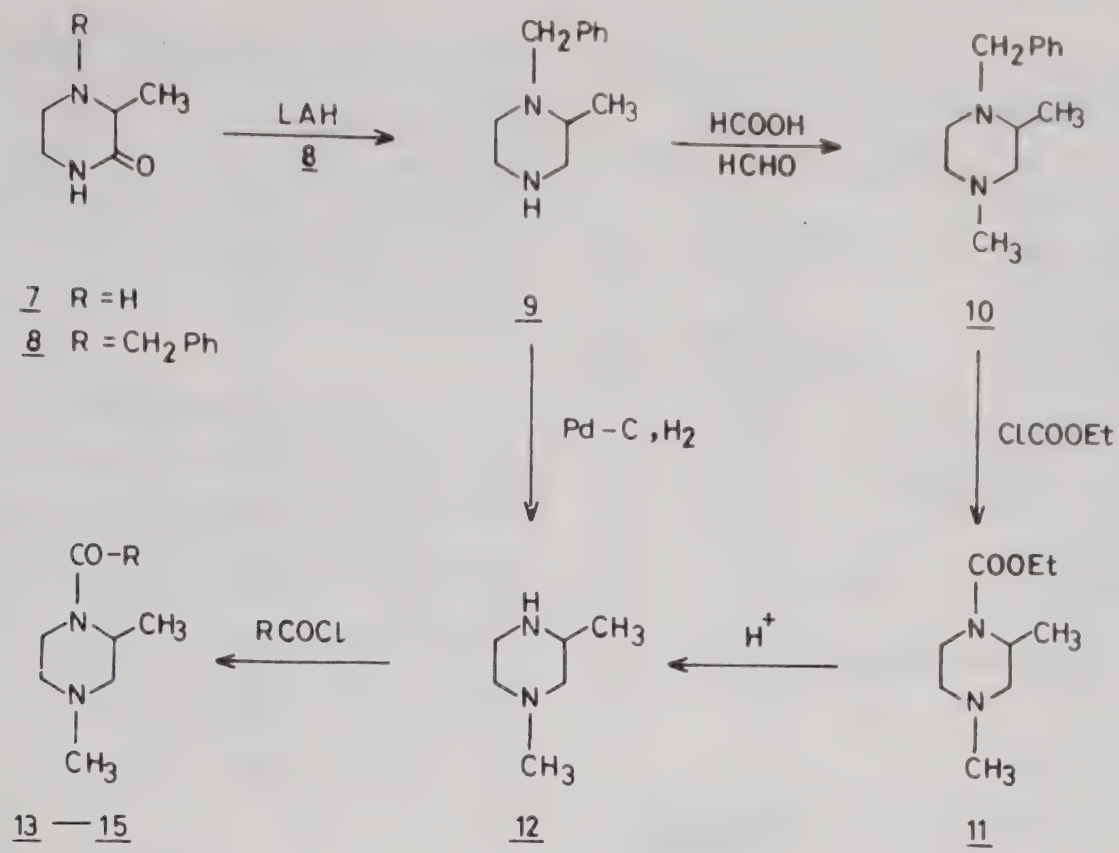



†CDRI Communication No. 3842

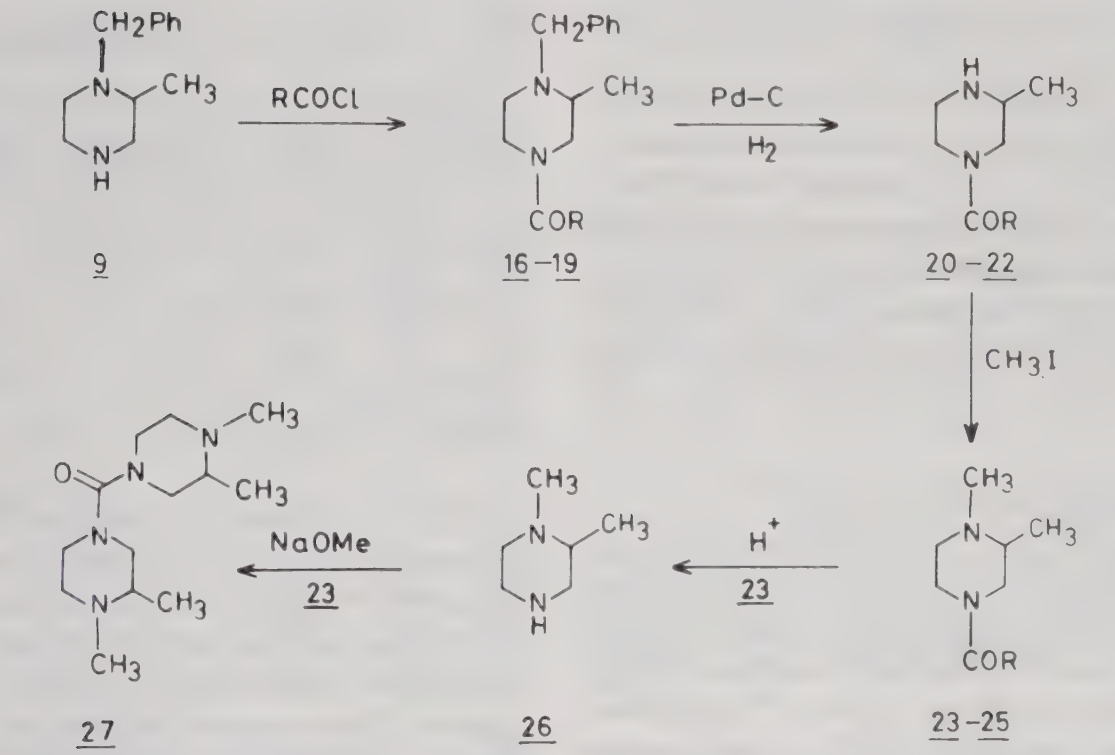
Condensation of 3-methylpiperazin-2-one (**7**)[4], prepared by treating ethylenediamine with ethyl β-bromopropionate, with benzyl chloride yielded 1-benzyl-2-methylpiperazin-2-one (**8**). Reduction of **8** with lithium aluminium hydride afforded 1-benzyl-2-methylpiperazine (**9**) which was methylated using formic acid-formaldehyde to give 1-benzyl-2,4-dimethylpiperazine (**10**) in a good yield. Reaction of **10** with ethyl chloroformate resulted in the formation of 1-carbethoxy-2,4-dimethylpiperazine (**11**) which was hydrolysed with dil. HCl to give 1,3-dimethylpiperazine (**12**). The latter was obtained more conveniently by hydrogenation of **10** over Pd-C. Treatment of **12** with various carbonyl chlorides yielded 1-substituted 2,4-dimethylpiperazines (**13-15**) (Scheme 1).

Reaction of **9** with different carbonyl chlorides afforded 1-benzyl-2-methyl-4-substituted-piperazines (**16-19**) which were debenzylated using Pd-C and hydrogen to form the corresponding debenzylated piperazines (**20-22**). Methylation of **20-22** with methyl iodide gave 1,2-dimethyl-4-substituted-piperazines (**23-25**) of which **23** was hydrolysed with dil. HCl to yield 1,2-dimethylpiperazine (**26**). Condensation of **26** with 4-carbethoxy-1,2-dimethylpiperazine (**23**) in the presence of sodium methoxide afforded 4-(1,2-dimethylpiperazin-4-ylcarbonyl)-1,2-dimethylpiperazine (**27**) (Scheme 2).

Reaction of 1-(chloroacetyl)-4-methylpiperazine (**28**)[5], prepared by condensing N-methylpiperazine with chloroacetyl chloride, with different amines gave 1-(aminoacetyl)-4-methylpiperazines (**29-31**) of which 1-(4-benzylpiperazin-1-ylacetyl)-4-methylpiperazine (**30**) was hydrogenated over Pd-C to form 1-(piperazin-1-ylacetyl)-4-methylpiperazine (**32**). Condensation of the latter with N,N-diethylcarbamoyl chloride yielded 1-[4-(N,N-diethylcarbamoyl)piperazin-1-ylacetyl]-4-methylpiperazine (**33**) while 1-N-benzimidazol-2-ylamino-acetyl)-4-




Scheme 1




Scheme 2

methylpiperazine (**34**) was obtained by treating **28** with 2-aminobenzimidazole (Scheme 3).

**Antifilarial Activity**

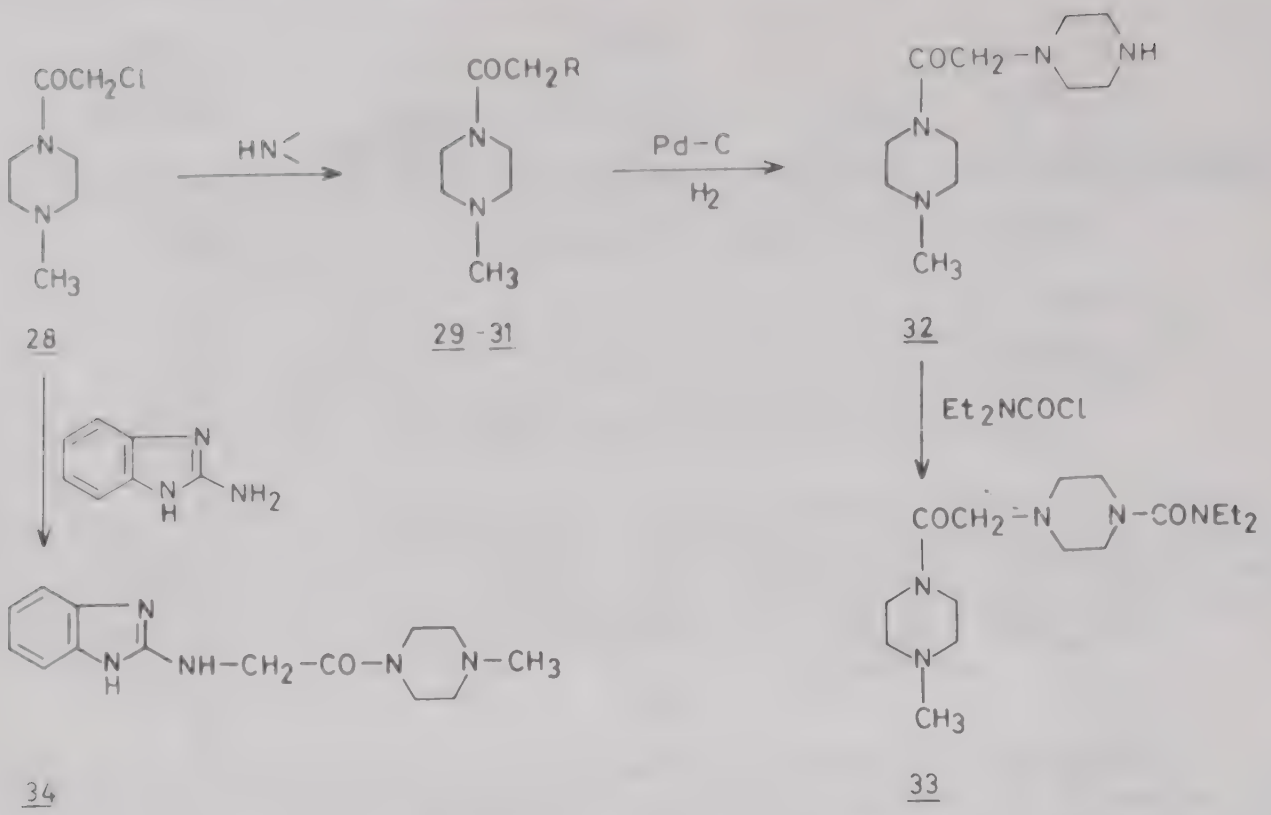
All the compounds were tested for their antifilarial activity against *Litomosoides carinii* infection in cotton rats by standard methods[6,7]. In this test none of the compounds was found to eliminate the microfilariae from the blood up to an intraperitoneal dose of 30 mg/kg given for 6 days.

**Experimental Procedure**

Structures of all the compounds were checked by IR spectra recorded on a Perkin-Elmer 137, 157 or 177 infracord spectrophotometer ($\nu_{max}$ in $cm^{-1}$). PMR spectra were recorded on a Varian A60-D or Perkin-Elmer R-32 spectrometer using TMS as internal reference (chemical shifts in δ, ppm). Purity of all the compounds was checked by TLC on silica gel G and basic alumina plates. The spots were located by iodine vapours or $KMnO_4$ spray. Melting points were taken in sulphuric acid-bath and are uncorrected.

3-*Methylpiperazin*-2-*one* (7)

A solution of ethyl 2-bromopropionate (18.0 g, 0.1




Scheme 3

mol) in methanol (100 ml) was added dropwise to a stirred solution of ethylenediamine (24.0 g, 0.4 mol) in methanol (100 ml) and the mixture refluxed for 2 hr, solvent removed, the residue treated slowly with ethanol (200 ml) and stirred at room temperature for 2 hr. The precipitated salt was removed by filtration and the filtrate concentrated *in vacuo* to get the product as an oil, yield 4.5 g (40%), b.p. 135°/3 mm (lit.[4], b.p. 135-36°/3 mm); IR (neat): 2900-3200 (NH), 1640 (CONH); PMR ($D_2O$): 1.62 (*d*, 3H, $CHCH_3$), 3.35-3.90 (*m*, 5H, $CH_3CH-NH-CH_2-CH_2$ NH).

1-*Benzyl*-2-*methylpiperazin*-3-*one* (**8**)

Benzyl chloride (1.20 g, 0.01 mol) was added to a solution of **7** (1.10 g, 0.01 mole) in methanol (40 ml) and the reaction mixture refluxed for 24 hr. The separated solid was filtered, washed with methanol (10 ml) and dried, yield 1.4 g (60%), m.p. 250-55°. The above hydrochloride was treated with 30% aq. ammonia to obtain the product as free base, yield 1.22 g (60%), m.p. 180°; IR(KBr) of **8** HCl: 3400 (NH), 1680 (CO); PMR($D_2O$) of **8**.HCl: 2.04 (*d*, 3H, $CHCH_3$), 3.7 (*s*, 2H, N-$CH_2$Ph), 3.89-4.53 (*m*, 5H, $CH_3CH-NH-CH_2-CH_2-NH$), 7.82 (*s*, 5H, Ar-*H*) (Found C, 70.6; H, 7.8; N, 13.8. $C_{12}H_{16}N_2O$ requires C, 70.6; H, 7.8; N, 13.7%).

1-*Benzyl*-2-*methylpiperazine* (**9**)

To a cooled and stirred suspension of lithium aluminium hydride (0.5 g, 0.012 mol) in anhyd. THF (200 ml) was added **8** portionwise under nitrogen atmosphere, and the reaction refluxed for 72 hr, solvent removed partially (150 ml) and the residue taken up in ether. The complex was decomposed by gradual addition of 10% aq. KOH solution with stirring and cooling. The separated inorganic mass was filtered, and the filtrate dried ($Na_2SO_4$) and concentrated *in vacuo* to yield the product as an oil which was purified over basic alumina column using chloroform as eluant, yield 1.3 g (70%); IR (neat): 3300 (NH), 2800-2900 ($CH_2$, $CH_3$); PMR($CDCl_3$): 1.10 (*d*, 3H, $CH-CH_3$), 1.90-2.95 (*m*, 7H, $CH_3-CH-CH_2-NH-CH_2-CH_2$), 3.13 (*d*, 2H, $CH_2$Ph), 7.25 (*s*, 5H, Ar-*H*) (Found: 75.8; H, 9.5; N, 14.7. $C_{12}H_{18}N_2$ requires C, 75.8; H, 9.5; N, 14.7%).

1-*Benzyl*-2,4-*dimethylpiperazine* (**10**)

Formaldehyde (38%, 2.5 ml) was added to a solution of **9** (1.90 g, 0.01 mol) in formic acid (2.5 ml) and the solution heated on a water-bath for 10 hr, solvent removed *in vacuo* and the residue basified by KOH solution. The separated oil was extracted with chloroform (2 × 50 ml), and the combined extracts dried ($Na_2SO_4$) and solvent removed to get the product as an oil which was purified on a basic alumina column using ethyl acetate as eluant, yield 1.19 g (59%); IR(neat): 2750-2900 ($CH_2$, $CH_3$); PMR ($CDCl_3$): 1.15 (*d*, 3H, $CH-CH_3$), 2.25 (*s*, 3H, $N-CH_3$), 2.30-3.40 (complex multiplet, 9H, $CH_3-CH-CH_2-N-CH_2-CH_2-N-CH_2$Ph), 7.25 (*s*, 5H, Ar-*H*) (Found: C, 76.5; H, 9.8; N, 13.7. $C_{13}H_{20}N_2$ requires C, 76.5; H, 9.8; N, 13.7%).

1-*Carbethoxy*-2,4-*dimethylpiperazine* (**11**)

A mixture of **10** (1.80 g, 0.01 mol) and ethyl chloroformate (3.25 g, 0.03 mol) in dry benzene (40 ml) was

refluxed for 48 hr. The reaction mixture was cooled and washed with 50% NaOH solution. The organic layer was dried ($Na_2SO_4$) and concentrated to yield the product as an oil which was purified on a basic alumina column using benzene as eluant, yield 0.43 g (25%); IR (neat): 1720 (CO) (Found C, 55.7; H, 8.1; N, 16.2. $C_9H_{18}N_2O_2$ requires C, 55.8; H, 8.2; N, 16.3%).

1,3-*Dimethylpiperazine* (**12**)

A solution of **11** (1.72 g, 0.01 mol) in 6*N* HCl (30 ml) was refluxed for 48 hr, solvent removed under reduced pressure, the residue basified with 50% NaOH solution and the separated oil extracted with benzene (2 × 50 ml). The combined extracts were dried ($Na_2SO_4$) and solvent was removed to get the product as an oil which was purified on a basic alumina column using chloroform as eluant, yield 0.8 g (66.6%); IR (neat): 3000 (NH), 2850-2900 ($CH_2$, $CH_3$); PMR (TFA): 1.40 (*d*, 3H, CH − C*H*$_3$), 2.90 (*s*, 3H, N − C*H*$_3$), 3.3-3.95 (*m*, 7H, N − C*H*$_2$ − C*H*$_2$ − NH − C*H*$_2$ − C*H* − CH$_3$) (Found: C, 63.1; H, 12.3; N, 24.6. $C_6H_{14}N_2$ requires C, 63.2; H, 12.3; N, 24.6%).

1-(*N,N-Dimethylcarbamoyl*)-2,4-*dimethylpiperazine* (**13**)

A mixture of **12** (1.2 g, 0.01 mol), N,N-dimethyl;carbamoyl chloride (1.02 g, 0.01 mol) and triethylamine (1.1 g, 0.01 mol) in dry benzene (30 ml) was refluxed for 6 hr. The reaction mixture was cooled and washed successively with saturated solutions of NaOH and NaCl. The benzene layer was dried ($Na_2SO_4$) and solvent removed to get the product as an oil which was passed through a basic alumina column using chloroform as eluant, yield 1.2 g (65%); IR (neat): 2700-3000 ($CH_2$), 1620 (CO); PMR ($D_2O$): 1.76 (*d*, 3H, CH − C*H*$_3$), 2.82 (*s*, 3H, $CH_2$ − N − C*H*$_3$), 3.02 [*s*, 6H, CON(C*H*$_3$)$_2$], 3.22-4.12 (*m*, 7H, CH − C*H*$_3$, N − CH$_2$ − CH$_2$ − N) (Found: C, 58.4; H, 10.2; N, 22.8; $C_9H_{19}N_3O$ requires C, 58.4; H, 10.3; N, 22.7%).

Using the above procedure, compounds **14** and **15** were obtained by treating **12** with cyclohexylcarbonyl chloride and N,N-diethylcarbamoyl chloride respectively.

Compounds **16-19** and **33** were also prepared similarly by condensing **9** and **32** with respective carbonyl chlorides. The characterization data of all these compounds are given in Table 1.

1-*Carbethoxy*-3-*methylpiperazine* (**20**)

A mixture of **16** (2.62 f, 0.01 mol) and 10% Pd-C (0.1 g) in gl. acetic acid (50 ml) was shaken with hydrogen at 2.5 kg/cm$^2$ pressure in a Paar hydrogenator for 12 hr. The catalyst was filtered off and solvent removed from the filtrate *in vacuo*. The residue was treated with 50% NaOH solution and the product extracted with benzene (2 × 100 ml). The combined extracts were dried ($Na_2SO_4$) and concentrated to give the desired compound as an oil which was purified on a basic alumina column using benzene as eluant, yield 1.20 g (70%); IR (neat): 1680 (CO); PMR ($D_2O$): 1.2-1.55 (*m*, 6H, CH − C*H*$_3$, CH$_2$ − C*H*$_3$), 2.7-3.8 (*m*, 6H, NH − C*H*$_2$ − C*H*$_2$ − N − C*H*$_2$), 4.10-4.45 (*m*, 3H, CH$_3$ − C*H*, C*H*$_2$ − CH$_3$) (Found: C, 55.9; H, 9.4; N, 16.3 $C_8H_{16}N_2O_2$ requires C, 55.9; H, 9.3; N, 16.3%).

Table 1 — Physical Data of the Compounds

| Compd | R | Mol. formula* | Nature of product† | Yield (%) |
|---|---|---|---|---|
| **14** | Cyclohexyl | $C_{13}H_{24}N_2O$ | Oil (a) | 44 |
| **15** | $NEt_2$ | $C_{11}H_{23}N_3O$ | Oil (b) | 40 |
| **16** | OEt | $C_{15}H_{22}N_2O_2$ | Oil (b) | 67 |
| **17** | Cyclohexyl | $C_{18}H_{28}N_2O$ | Oil (a) | 60 |
| **18** | $NMe_2$ | $C_{15}H_{23}N_3O$ | Oil (b) | 60 |
| **19** | $NEt_2$ | $C_{17}H_{27}N_3O$ | Oil (b) | 65 |
| **21** | $NMe_2$ | $C_8H_{17}N_3O$ | Oil (b) | 68 |
| **22** | $NEt_2$ | $C_{10}H_{21}N_3O$ | Oil (a) | 64 |
| **23** | OEt | $C_9H_{18}N_2O_2$ | Oil (c) | 63 |
| **25** | $NEt_2$ | $C_{11}H_{23}N_3O$ | Oil (a) | 60 |
| **29** | 3-Methylpiperidin-1-yl | $C_{13}H_{25}N_3O$ | Oil (b) | 56 |
| **30** | 4-Benzylipiperazin-1-yl | $C_{18}H_{28}N_4O$ | Oil (b) | 58 |
| **32** | — | $C_{11}H_{22}N_4O$ | Oil (b) | 50 |
| **33** | — | $C_{16}H_{31}N_5O_2$ | Oil (a) | 52 |

*All the compounds were analysed for C, H and N and the results were within ±0.5% of the calculated values.
†All the oils were purified on a basic alumina column. The eluants used in each case is given in parenthesis; a = chloroform, b = benzene, c = ethyl acetate.

Similarly, compounds **21** and **22** (Table 1) were prepared by hydrogenation of **18** and **19** respectively. Compounds **12** and **32** were also obtained in a similar manner by Pd-C hydrogenation of **9** and **29** respectively.

1,2-*Dimethyl*-4-(*N,N-dimethylcarbamoyl*)-*piperazine* (**24**)

A mixture of **21** (1.7 g, 0.01 mol), methyl iodide (4.3 g, 0.03 mol) and triethylamine (1.01 g, 0.01 mol) in dry acetone (40 ml) was stirred at room temperature for 48 hr, solvent removed completely, and the residue taken up in benzene and washed with a saturated solution of NaCl. The organic layer was dried ($Na_2SO_4$) and solvent removed *in vacuo* to obtain the product as an oil which was purified on a basic alumina column using chloroform as eluant, yield 1.25 g (68%); IR (neat): 2800-3000 ($CH_2$, $CH_3$), 1640 (CO); PMR (TFA): 1.22 (*d*, 3H, CH − C*H*$_3$), 2.82 [complex multiplet, 16H, N − CH$_3$, CON(CH$_3$)$_2$, CH$_3$ − C*H* − CH$_2$, N − C*H*$_2$ − C*H*$_2$ − NCH$_3$] (Found: C, 58.3; H,

10.4; N, 22.8. $C_9H_{19}N_3O$ requires C, 58.4; H, 10.3; N, 22.7%).

Similarly compounds **23** and **25** (Table 1) were prepared by methylation of **20** and **22** respectively with methyl iodide.

1,2-*Dimethylpiperazine* (**26**)

A mixture of **23** (1.8 g, 0.01 mol) and dil. HCl (10 ml) was refluxed for 24 hr. Solvent was removed *in vacuo*, and the residue taken up in benzene and treated with 50% NaOH solution. The organic phase was separated, dried ($Na_2SO_4$) and concentrated to get the product as an oil which was purified on a basic alumina column using benzene as solvent, yield 0.69 g (61%); IR (Neat): 3400 (NH), 2700-3000 ($CH_2$, $CH_3$); PMR ($D_2O$): 1.45 (*d*, 3H, $CH-CH_3$), 2.82 (*s*, 3H, $N-CH_3$), 3.15-3.86 (*m*, 7H, $CH_3-CH$, $N-CH_2-CH_2-N-CH_2$) (Found: C, 63.2; H, 12.3; N, 24.6. $C_6H_{14}N_2$ requires C, 63.2; H, 12.3; N, 24.6%).

4-(1,2-*Dimethylpiperazin*-4-*ylcarbonyl*)-1,2-*dimethylpiperazine* (**27**)

A solution of **26** (1.8 g, 0.01 mol) in abs. methanol (20 ml) was added dropwise to a stirred solution of **23** (1.8 g, 0.01 mol) and sodium methoxide (from 0.3 g sodium) in methanol (40 ml), and the resulting mixture stirred for 12 hr, solvent removed *in vacuo* and the residue extracted with benzene (3 × 50 ml). The combined extracts were washed with saturated solution of NaCl, dried ($Na_2SO_4$) and concentrated to get the product as an oil which was purified on basic alumina column using benzene as eluant, yield 1.60 g (63%); IR (neat): 1620 (CO); PMR ($CDCl_3$): 1.1 [*d*, 6H, $(CH-CH_3)_2$], 2.15 [*s*, 6H, $(N-CH_3)_2$], 2.2-2.55 [*m*, 6H, $(N-CH-CH_3)_2$, $(CH_3-N-CH_2)_2$], 2.6-2.9 [*m*, 8H, $[CON(CH_2CH_2)_2]$] (Found: C, 61.5; H, 10.3; N, 22.1. $C_{13}H_{26}N_4O$ requires C, 61.4; H, 10.2; N, 22.0%).

1-*Chloroacetyl*-4-*methylpiperazine* (**28**)

A solution of chloroacetyl chloride (1.12 g, 0.01 mol) in dry benzene (40 ml) was added dropwise to a cooled and stirred mixture of N-methylpiperazine (1.0 g, 0.01 mol) and triethylamine (1.10 g, 0.01 mol) in dry benzene (40 ml). The reaction mixture was stirred at room temperature for 12 hr and worked-up as usual, yield 1.1 g (62%), m.p. 122° (lit.[5], m.p. 124-26°).

1-(*Pyrrolidin*-1-*ylacetyl*)-4-*methylpiperazine* (**31**)

A mixture of **28** (1.76 g, 0.01 mol), pyrrolidine (0.85 g, 0.01 mol) and triethylamine (1.1 g, 0.01 mol) in dry benzene (40 ml) was refluxed for 12 hr, diluted with benzene (40 ml) and washed with a saturated solution of NaCl. The organic phase was dried ($Na_2SO_4$) and solvent removed *in vacuo* to get the product as an oil which was purified over a basic alumina column using benzene as eluant, yield 1.05 g (50%); IR (neat): 1680 (CO); PMR ($CCl_4$): 1.5-2.0 (*m*, 4H, $CH_2-CH_2$), 2.12-2.5 [*m*, 11H, $CH_2-N-(CH_2)_2$, $CH_3-N-(CH_2)_2$], 3.01 (*s*, 2H, $COCH_2-N$), 3.15-3.68 [*m*, 4H, $CON(CH_2)_2$] (Found, C, 58.1; H, 5.8; N, 14.3. $C_{11}H_{21}N_3O$ requires C, 58.1; H, 5.8; N, 14.2%).

By a similar method, compounds **29** and **30** (Table 1) were prepared by treating **28** with 3-methylpiperidine and 1-benzylpiperazine respectively.

1-(*N-Benzimidazol*-2-*ylaminoacetyl*)-4-*methylpiperazine* (**34**)

A mixture of **28** (1.76 g, 0.01 mol), 2-aminobenzimidazole (1.8 g, 0.01 mol) and triethylamine (1.1 g, 0.01 mole) chloroform (100 ml) was refluxed for 24 hr, cooled and washed with water. The organic layer was separated, dried ($Na_2SO_4$) and concentrated *in vacuo* to get a solid which was crystallised from chloroform, yield 1.36 g (50%), m.p. 177°; IR(KBr): 1680 (CO) (Found C, 61.7; H, 6.8; N, 25.5. $C_{14}H_{19}N_5O$ requires C, 61.5; H, 7.0; N, 25.6%).

## Acknowledgement

The authors thank Drs R K Chatterjee and A B Sen of the Parasitology Division of this institute for providing the antifilarial test results. One of them (ESC) is grateful to UGC, New Delhi for financial support.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 757-760

# Studies on β-Carbolines: Synthesis of 2-, 3- & 6-Substituted 9*H*-Pyrido[3,4-*b*]indoles as Tubal Occluding Agents +

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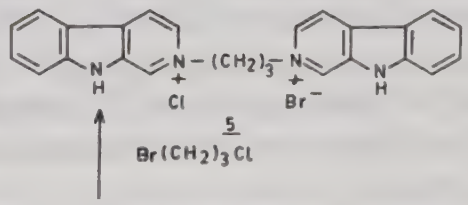
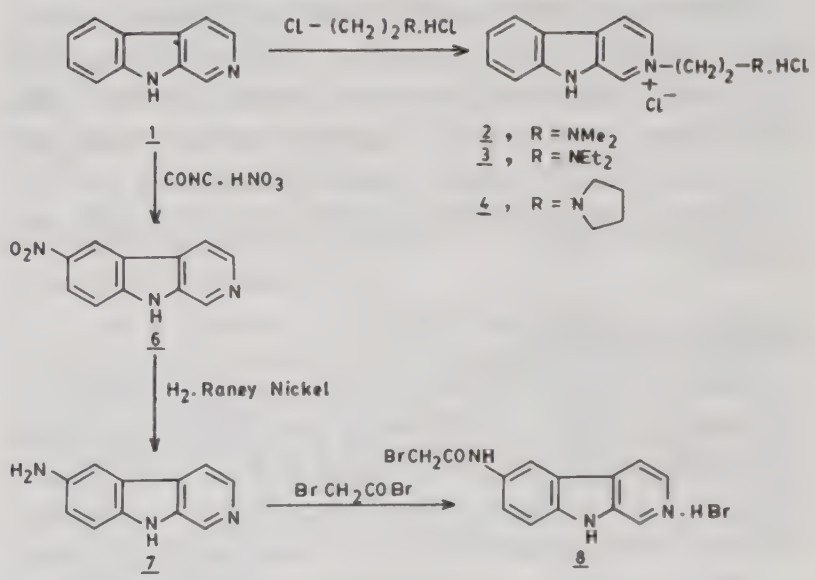
*Received* 12 *December* 1986; *accepted* 6 *March* 1987

2-Substituted quaternary ammonium 9*H*-pyrido[3,4-*b*]-indole derivatives (**2-4**) have been obtained by the condensation of 9H-pyrido[3,4-*b*]indole (**1**) with aminoalkyl chloride hydrochlorides. 3- and 6-Bromoacetamido-9H-pyrido[3,4-b]indole hydrobromides (**8/19**) have been synthesized by the reaction of bromoacetyl bromide with corresponding 3-/6-amino-9*H*-pyrido[3,4-*b*]indoles. The reaction of phenyl isothiocyanate on 9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid hydrazide (**9**) leads to the corresponding thiosemicarbazide (**10**), which on cyclisation with 4% aq NaOH affords the triazine (**11**). **11** on reaction with $C_2H_5I$ and $ClCH_2COOH$ affords ethyl mercaptotriazine (**12**) and carboxymethylmercaptotriazine (**13**) respectively. The ethylsulphonyltriazine (**14**) has been prepared by the oxidation of ethyl mercaptotriazine (**11**) while benzylidene derivative (**15**) has been obtained by condensation of $C_6H_5CHO$ with hydrazide (**9**). Condensation of azide **16** with glycine furnishes 9*H*-pyrido[3,4-*b*]indole-3-carbonylglycine (**17**). Compounds **1** and **11** produce 100% blockade in fallopian tubes of rhesus monkey and mice respectively.

The use of variety of chemicals for inducing closure of fallopian tube as an alternative to surgical tubectomy was first studied by Zipper *et al.*[1]. In subsequent studies it was demonstrated that quinacrine is effective in inducing fallopian tube occlusion in monkey and humans[2–4]. The major drawback in the use of quinacrine was the toxicity of acridines observed in case of rats and rabbits[5,6] and its potential tetratogenicity as a result of binding with genetic material[7]. These observations led us to search for non-acridine based compounds, which may serve as possible fallopian tube occluding agents. In initial exploration we synthesized 3-amino-9*H*-pyrido[3,4-*b*]indole[8] (**18**), which successfully closed both the fallopian tubes of female rhesus monkeys. These results prompted us to synthesise a variety of analogs having β-carboline moiety as tubal occluding agents. The synthesis and tubal occluding activity of these compounds are reported in this paper.

9*H*-Pyrido[3,4-*b*]indole (**1**) on quaternisation with various amino alkyl chloride hydrochlorides in 2-propanol yielded the corresponding quaternary alkyl amino-9*H*-pyrido[3,4-*b*]indole hydrochlorides (**2-4**) while the condensation of **1** with 1-bromo-3-chloropropane in 2-propanol provided the bis-quaternary derivative (**5**). The amino compounds (**7/18**) on reaction with bromo acetyl bromide in dry DMF afforded 3-/6-bromoacetamido-9*H*-pyrido[3,4-*b*]indole hydrobromides (**8/19**) in 65% yield (Scheme 1).




SCHEME 1

The reaction of phenyl isothiocyanate on 9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid hydrazide (**9**) yielded the thiosemicarbazide (**10**), which on cyclization in 4% aq NaOH gave the triazine (**11**), while the attempted cyclization in dil $H_2SO_4$ resulted in decomposition of the compound. The 3-(2-N-phenyl-3-mercapto-2,4,5-triazolyl)-9*H*-pyrido(3,4-b)indole (**11**) on condensation with ethyl iodide and chloroacetic acid afforded the required ethylmercaptotriazine (**12**) and carboxymethylmercaptotriazine (**13**) respectively. Ethylsulphonyltriazine (**14**)

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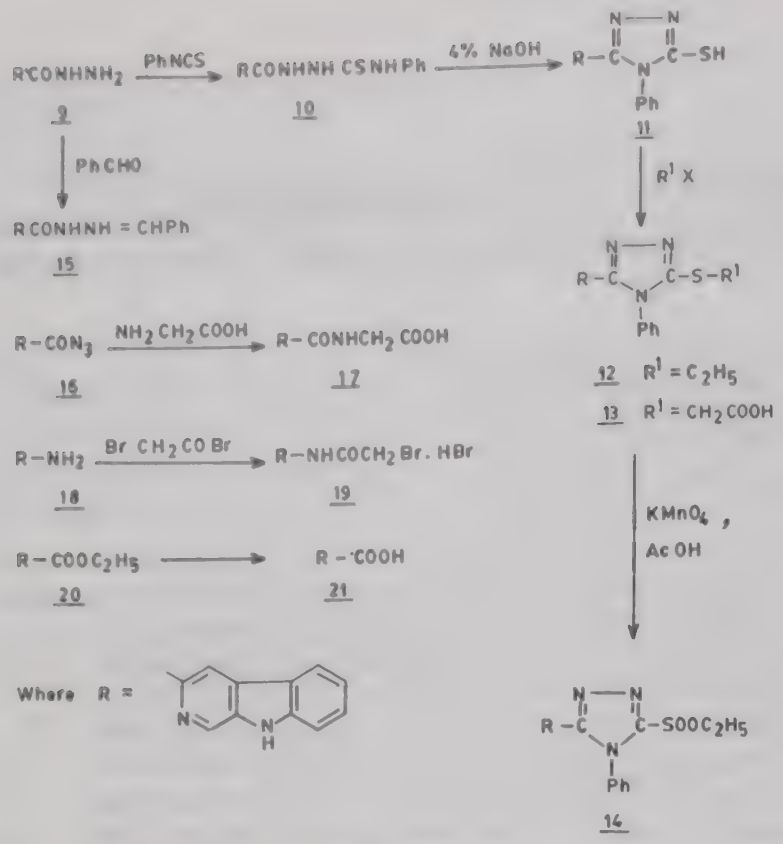


SCHEME 2

was synthesized by the oxidation of **12** with $KMnO_4$ in acetic acid. Condensation of the hydrazide (**9**) with benzaldehyde in ethanol gave the $N^1$-benzylidene-9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid hydrazide (**15**) (Scheme 2).

9*H*-Pyrido[3,4-*b*]indole-3-carbonylglycine (**17**) was prepared by the reaction of glycine and 9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid azide (**16**). Surprisingly α-alanine, β-alanine and L-serine did not react with **16** under similar conditions and instead gave 9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (**21**).

**Biological activity**

Most of the compounds were tested for tubal occluding activity; **10-15** were also tested for vasal occluding activity. Compounds **1**, **6**, **7** and **9** were also tested for their acute toxicity, gross observational effects, reduction in spontaneous and forced locomotor activity, amphetamine hyperactivity and amphetanine toxicity in aggregated animals and electroshock seizures in male mice at 0.2 $LD_{50}$ by standard methods. Effect on blood pressure and respiration was studied in anaesthetized cats by administering 2.5 mg/kg i.v. of the compounds. The compounds were also screened for diuretic activity (chlorothiazide as standard) and passive cutaneous anophylaxis (PCA) inhibitory properties at 0.2 $LD_{50}$ by methods described earlier[12].

Two of the compounds, viz. **1** and **11** produced 100% blockade in both the fallopian tubes of female rhesus monkeys and in mice respectively. None of the tested compounds (**10-15**) showed vasal occluding activity in mice. These observations suggest that functionalisations at 2-/6-position of 9*H*-pyrido[3,4-*b*]indole and at 3-position by groups other than $NH_2$, $COOCH_3$ and 2-N-phenyl-3-mercapto-2,4,5-triazolyl do not result in producing active compounds thus pointing towards the presence of flattened area with reactive functionalities as essential structural requirement for this activity.

Apart from this, the four compounds (**1**, **6**, **7**, **9**) tested for CNS/CVS activities were well tolerated in animals as evidenced by their approximate $LD_{50}$ values and were depressant in gross behaviour, except **7** which was stimulant. None of them showed very promising activity except mild diuretic, anti-PCA and CNS depressant activity.

**Experimental Procedure**

Melting points were determined in an electrically heated apparatus and are uncorrected. Compounds were routinely checked by IR spectra in KBr on a Perkin-Elmer infracord ($\nu_{max}$ in $cm^{-1}$), PMR spectra on a Varian A-60D instrument (TMS as internal reference and chemical shifts in $\delta$ ppm) and TLC on silica gel or alumina plates. Microanalyses of each compound were found within ± 0.4% of required values.

*9H-Pyrido[3,4-b]indole* (**1**)

This was prepared with a modified literature method[9]. A solution of $K_2Cr_2O_7$ (125 g) and gl acetic acid (150 ml) in distilled water (1000 ml) was added to the refluxing solution of 1,2,3,4-tetrahydro-9*H*-pyrido(3,4-*b*)indole-3-carboxylic acid (20 g, 0.0926 mol) in gl. acetic acid and distilled water (800 ml). The reaction mixture was refluxed for additional 1 hr, cooled and filtered. The precipitate was suspended in water (200 ml), neutralized with 50% aq $Na_2CO_3$ and extracted with hot ethyl acetate (3 × 250 ml). The organic layer was dried ($Na_2SO_4$) and concentrated to give **1**, which recrystallised from ethyl acetate, yield 8.6 g (55.3%) m.p. 199° (lit.[9], 199-201°C).

*2-β-(N,N-Dimethylamino)ethyl-9H-pyrido*[3,4-*b*]*indole hydrochloride* (**2**)

A mixture of **1** (1.68 g, 0.01 mol) and N,N-dimethylaminoethyl chloride hydrochloride (1.44 g, 0.01 mol) in propan-2-ol (20 ml) was refluxed for 3 hr. The separated solid was filtered, washed with cold propan-2-ol, yield 1.1 g (35.3%), m.p. 250°; IR: 3430, 2950, 2800, 1640, 760, 730.

*2-β-(N,N-Diethylamino)ethyl-9H-pyrido*(3,4-*b*)*indole chloride hydrochloride* (**3**)

Experimental procedure similar to **2**; yield 1.2 g (35.3%), m.p. 225°C.

2-*β*-(*N*-*Pyrrolidino*)*ethyl*-9*H*-*pyrido*(3,4-*b*)*indole chloride hydrochloride* (**4**)

Method similar to **2**; yield 1.2 g (35.3%) m.p.276°C.

1,3-*Bis*{2,2′-*pyrido*[3,4-*b*]*indole*}*propane bromide chloride* (**5**)

1-Bromo-3-chloropropane (0.788 g, 0.005 mol) was added to a solution of **1** (1.68 g, 0.01 mol) in propan-2-ol (20 ml) and mixture was refluxed for 16 hr. Compound **5** which separated out as a crystalline solid on cooling, was filtered off, yield 1.5 g (60.7%), m.p.265-70°: IR: 3350-3000, 1630, 750, 730; PMR(TFA): 8.85 (*s*, 2H, $H_1$ and $H_{1'}$), 8.13-7.67 (*m*, 6H, $H_3$, $H_4$, $H_8$, $H_{3'}$, $H_{4'}$ and $H_{8'}$), 7.5-6.83 (*m*, 6H, $H_5$-$H_7$ and $H_{5'}$-$H_{7'}$), 4.72 (*m*, 4H, 2N-$CH_2$), 2.75 (*m*, 2H, $CH_2$).

6-*Bromoacetamido*-9*H*-*pyrido*[3,4-*b*]*indole hydrobromide* (**8**)

A solution of **7**[10] (0.915 g, 0.005 mol) in dry N,N-dimethylformamide (5 ml) was added dropwise to stirred bromoacetyl bromide (0.5 ml, 0.0055 mol) at −10°C. Stirring was continued for two hr at room temperature and solvent removed *in vacuo* to give **8**, which crystallised from methanol-ether, yield 1.2 g (65%), m.p.225°(d), IR: 1670; PMR(TFA): 9.02 (*s*, 1H, $H_1$), 8.7 (*d*, 1H, $H_3$, $J$=7 Hz), 8.38 (*d*, 1H, $H_4$), 8.03 (*m*, 2H, $H_7$ and $H_8$), 7.68 (*s*, 1H, NH), 7.32 (*s*, 1H, $H_5$), 3.83 (*s*, 2H, $CH_2$).

1-[3-(9*H*-*Pyrido*[3,4-*b*]*indolyl*)]-*carboxyl*-4-*phenyl thiosemicarbazide* (**10**)

A mixture of 9H-pyrido[3,4-*b*]indole-3-carboxylic acid hydrazide[11] (1.13 g, 0.005 mol) and phenyl isothiocyanate (0.675 g, 0.005 mol) in ethanol (20 ml) was refluxed for 2 hr, cooled, separated solid filtered and crystallised from ethanol to afford **10**, yield 1.3 g (72%), m.p. > 360°; IR: 1660, 1255, 742, 710; PMR(TFA): 8.80 (2*s*, 2H, $H_1$ and $H_4$), 7.95 (*d*,, 1H, $H_8$, $J$=7 Hz), 7.42 (*m*, 2H, $H_6$ and $H_7$), 7.3 (*m*, 1H, $H_5$), 7.07 (*s*, 5H, Ar-H).

3-[2-*N*-*Phenyl*-3-*mercapto*-2,4,5-*triazolyl*]-9*H*-*pyrido*[3,4-*b*]*indole* (**11**)

**10** (0.9 g, 0.0025 mol) was dissolved in 4% aq NaOH (10 ml), the solution refluxed for 2 hr, cooled, acidified with dil. HCl, filtered, the precipitate washed with water and crystallized from ethanol to give **11**, yield 0.7 g (82.4%), m.p. > 360°; IR: 1625, 742, 690; PMR(TFA): 7.85 (*bs*, 1H, indole-NH), 7.43 (*s*, 5H, Ar-H), 7.3-6.97 (*m*, 5H, $H_1$, $H_5$-$H_8$), 6.37 (*s*, 1H, $H_4$), 5.8 (*s*, 1H, SH).

3-[2-*N*-*Phenyl*-3-*ethylmercapto*-2,4,5-*triazolyl*]-9*H*-*pyrido*[3,4-*b*]*indole* (**12**)

A mixture of **11** (0.343 g, 0.001 mol) and ethyl iodide (0.136 g, 0.01 mol) in 10% alcoholic NaOH (10 ml) was refluxed for 2 hr, cooled, diluted with water and filtered to give **12**, which crystallized from ethanol, yield 0.35 g (94.6%), m.p.212°; PMR(TFA): 7.8 (*s*, 1H, indole −NH), 7.7-6.92 (*m*, 11-H, ArH), 3.22 (*q*, 2H, $CH_2$, $J$=8 Hz), 1.17 (*t*, 3H, $CH_3$).

3-[2-*N*-*Phenyl*-3-*carboxymethylmercapto*-2,4,-*triazolyl*]-9*H*-*pyrido*[3,4-*b*]*indole* (**13**)

Chloroacetic acid (0.095 g, 0.001 mol) was added to a solution of **11** (0.343 g, 0.001 mol) in 8% aq NaOH (10 ml) and refluxed for 2 hr. On cooling and acidification with dil HCl, the separated solid (**13**) was filtered, washed with water and recrystallised from ethanol, yield 0.3 g (75%), m.p.210°C; PMR(TFA): 8.88 (*s*, 1*H*, *indole NH*), 7.7-7.2 (*m*, 11H, Ar-H), 3.95 (*s*, 2H, $CH_2$).

3-[2-*N*-*Phenyl*-3-*ethylsulphonyl*-2,4,5-*triazolyl*]-9*H*-*pyrido* [3,4-*b*]*indole* (**14**)

Potassium permanganate was added in small portions to a refluxing solution of **12** (1.113 g, 0.003 mol) in gl. AcOH (10 ml), till $KMnO_4$ colour persisted. Refluxing was continued for 2 hr, cooled, diluted with water and extracted with $CHCl_3$. Organic layer was washed with water, dried ($Na_2SO_4$) and concentrated to give **14**, which crystallized from ethanol-ether, yield 0.45 g (37.5%), m.p. 172°; PMR($CDCl_3$): 8.5 (*s*, 1H, $H_1$), 8.33 (*s*, 1H, $H_4$), 7.8 (*d*, 1H, $H_8$, $J$=7 Hz), 7.5-7.0 (*m*, 8H, Ar-H), 3.15 (*q*, 2H, $CH_2$, $J$=7 Hz), 1.3 (*t*, 3H, $CH_3$).

*N*[1]-*Benzylidene*-9*H*-*pyrido*[3,4-*b*]*indole*-3-*carboxylic acid hydrazide* (**15**)

It was prepared similarly as described for **10** except that benzaldehyde was used instead of phenyl isothiocyanate, yield 1.5 g (95%), m.p. 310-12°; IR: 1656; PMR(TFA): 8.36 (*bs*, 1H, indole NH), 8.08-7.8 (*m*, 3H, $H_1$, $H_4$ and $H_8$), 7.5 (*s*, 5H, Ar-H), 7.1 (*m*, 2H, $H_6$ and $H_7$), 6.9 (*s*, 1H, $H_5$), 6.3 (*s*, 1H, CH), 5.7 (*s*, 1H, NH).

9*H*-*Pyrido*[3,4-*b*]*indole*-3-*carbonyl*-*N*-*glycine* (**17**)

9H-Pyrido[3,4-*b*]indole-3-carboxylic acid azide[11] (**16**) (2.37 g, 0.01 mol) was added in small portions to a stirred solution of glycine (0.75 g, 0.01 mol) in 2% aq NaOH (20 ml) at −5°C. Stirring was continued for 6 hr at room temperature, suspended impurities were removed by filtration, the filtrate was acidified with acetic acid, filtered and residue was washed with water to give **17**, crystallized from ethanol, yield 1.4 g (52%), m.p. 261°; IR: 1710, 1670; PMR(DMSO-$d_6$): 8.58 (*s*, 2H, $H_1$ and indole −NH), 8.03 (*d*, 1H, $H_8$, $J$=7 Hz), 7.33 (*m*, 2H, $H_4$ and $H_7$),

7.17-6.17 (*m*, 4H, $H_5$, $H_6$, NH, OH), 4.15 (*d*, 2H, $CH_2$).

*3-Bromoacetamido-9H-pyrido[3,4-b]indole hydrobromide* (**19**)

It was prepared by a similar procedure as reported for **8** except that 3-amino-9*H*-pyrido[3,4-*b*]indole[11] (**18**) was used instead of **7**, compound **19** was crystallized from methanol-ether, yield 1.3 g (67.5%), m.p. 180-82°; IR: 1670; PMR(DMSO-$d_6$): 8.92 (*s*, 1H, indole −NH), 8.67 (*s*, 1H, NH), 8.33-8.00 (*m*, 2H, $H_1$ and $H_4$), 7.93-7.07 (*m*, 4H, $H_5$-$H_8$), 3.97 (*s*, 2H, $CH_2$).

*9H-Pyrido[3,4-b]indole-3-carboxylic acid* (**21**)

A mixture of methyl 9H-pyrido[3,4-*b*]indole-3-carboxylate (0.5 g), conc. HCl (6 ml) and ethanol (6 ml) was refluxed for 4 hr, cooled, basified with aq $NH_4OH$. Solid filtered off washed with water and crystallized from ethanol, yield 0.4 g (85.3%), m.p.170°; IR: 1710; PMR(TFA): 8.87-8.75 (*m*, 3H, $H_1$, $H_4$ and indole −NH), 8.05 (*d*, 1H, $H_8$, $J$= 7 Hz), 7.58-7.09 (*m*, 4H, $H_5$-$H_7$ and OH).

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 761-765

# Synthesis of N-[3-Aryl(thio/sulphono)propyl]heterocyclics as Potential CNS/CVS Agents†

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*Received* 8 *September* 1986; *accepted* 16 *January* 1987

A number of N-[3-aryl(thio/sulphono)propyl]heterocyclics (**6-13**, **19-21**) have been synthesized by the condensation of γ-chloropropylaryl sulphides and sulphones (**3-5** and **18**) with appropriate nitrogen heterocyclics. The 4-aminophenyl derivatives in case of sulphides (**14-17**) and sulphones (**22-24**) have been prepared by hydrolysis of the corresponding 4-acetamidophenyl derivatives (**6-9, 19-21**). The 4-amino- or 4-fluorosulphone (**27/30**) has been obtained by the condensation of the corresponding γ-chloropropyl 4-amino/fluorophenyl sulphone (**26/29**) with octahydropyrazinopyridoindole, the former (**26**) being obtained by the hydrolysis of **18** while **29** from **26** by decomposition of its diazonium salt (**28**). These compounds in general exhibit good hypotensive activity in addition to other activities like antiinflammatory, PCA, diuretic and anxiolytic.

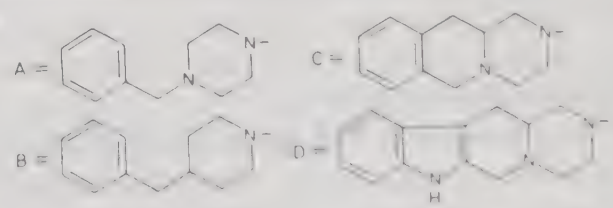
Certain octahydropyrazinopyridoindoles, pyrazinoquinolines, pyrazinoisoquinolines, piperazines and piperidines have been found to possess a wide spectrum of biological activities[1-6], including hypotensive activity. In addition, antihypertensive activity is also observed in compounds containing thio or sulphono groups, such as 1,2,4-benzothiadiazine-1,1-dioxides[7,8], 2-(2-methylthioethylamino)ethylguanidine[9], thiadiazoles[10] and some sulphur containing analogues of phenylpropylamines[11]. In an attempt to dissociate hypotensive activity in case of substituted piperazines, particularly octahydropyrazinopyridoindoles and pyrazinoisoquinolines it was considered of interest to synthesise some aryl(thio/sulphono)propyl derivatives of pyrazinopyridoindole, pyrazinoisoquinoline, piperazine and piperidine. The present paper describes the synthesis and hypotensive activity of these compounds.

The required γ-chloropropyl 4-substitutedphenyl sulphides (**3-5**) were prepared by the condensation of the corresponding thiophenols (**2**) with 1-bromo-3-chloropropane (**1**) in the presence of NaOH in ethanol. The γ-chloropropyl 4-acetamidophenyl sulphide (**3**) was oxidised to the corresponding sulphone (**18**) with potassium permanganate in gl. acetic acid. Condensation of these thio and sulphono compounds with appropriate heterocyclics in dry DMF in the presence of $Na_2CO_3$ and NaI afforded the desired 4-substi-

Table 1—Charac' risation Data of Various Compounds Prepared

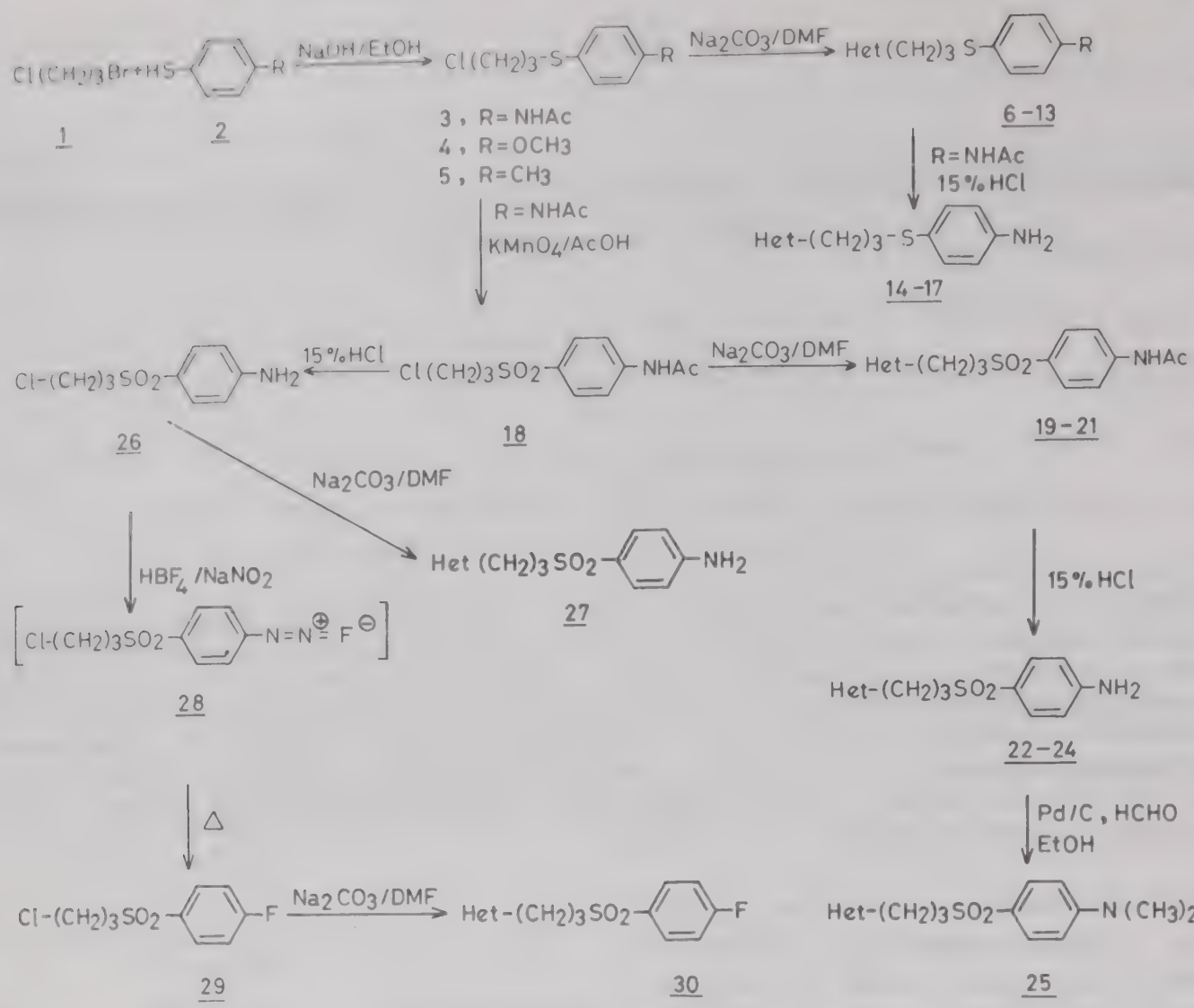
| Compd | Het[a] | R | Mol. formula | m.p. °C | Yield (%) |
|---|---|---|---|---|---|
| **6** | A | NHAc | $C_{22}H_{24}N_3OS$ | 68-70[b] | 48 |
| **7** | B | NHAc | $C_{23}H_{30}N_2OS$ | 50[c] | 44 |
| **8** | C | NHAc | $C_{23}H_{29}N_2OS.HCl$ | 145[d] | 70 |
| **9** | D | NHAc | $C_{25}H_{30}N_4OS$ | 85[e] | 76 |
| **10** | C | $OCH_3$ | $C_{22}H_{28}N_2OS$ | 64[f] | 60 |
| **11** | D | $OCH_3$ | $C_{24}H_{29}N_3OS$ | 164[e] | 80 |
| **12** | C | $CH_3$ | $C_{22}H_{28}N_2S$ | 42[g] | 56 |
| **13** | D | $CH_3$ | $C_{24}H_{29}N_3S$ | 158[e] | 58 |
| **14** | A | $NH_2$ | $C_{20}H_{27}N_3S.HCl$ | 210[d] | 78 |
| **15** | B | $NH_2$ | $C_{21}H_{28}NS.HCl$ | 202[d] | 56 |
| **16** | C | $NH_2$ | $C_{21}H_{27}N_3S.HCl$ | 190[d] | 71 |
| **17** | D | $NH_2$ | $C_{23}H_{28}N_4S$ | 90[e] | 90 |
| **19** | A | NHAc | $C_{22}H_{29}N_3O_3S.HCl$ | 189-90[d] | 40 |
| **20** | B | NHAc | $C_{23}H_{30}N_2O_3S$ | 97[e] | 83 |
| **21** | C | NHAc | $C_{23}H_{29}N_3O_3S$ | 53[f] | 66 |
| **22** | A | $NH_2$ | $C_{20}H_{27}N_3O_2S$ | 98-99[d] | 56 |
| **23** | B | $NH_2$ | $C_{21}H_{28}N_2O_2S$ | 90[e] | 58.8 |
| **24** | C | $NH_2$ | $C_{21}H_{27}N_3O_2S$ | 60[f] | 83.3 |
| **25** | C | $N(CH_3)_2$ | $C_{23}H_{31}N_3O_2S$ | 93[d] | 63 |
| **27** | D | $NH_2$ | $C_{23}H_{28}N_4O_2S$ | 230[c] | 48 |
| **30** | D | F | $C_{23}H_{26}FN_3O_2S$ | 158[e] | 54 |

[a]




[b]Benzene-hexane; [c]Chloroform; [d]Ethanol; [e]Benzene; [f]Ether; [g]Ether-hexane.
For preparation of C and D see ref. 4 and 1.

†CDRI Communication No. 3903




Scheme 1

tuted-phenyl(thio/sulphono) derivatives (**6-13**, **19-21**, **27**). The corresponding 4-amino derivatives (**14-17**, **22-24** and **26**) were obtained by the acidic hydrolysis of **6-13**, **19-21** and **18** respectively (Scheme 1, Table 1). The 1-(1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-2-yl)-3-(4-aminophenylsulphono)propane (**21**) on reductive alkylation in the presence of ethanol, formaldehyde and Pd/C gave the corresponding 4-dimethylamino derivative (**25**). The 1-(1,2,3,4,6,7,12,12a-octahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indol-2-yl)-3-(4-fluorophenylsulphono)propane (**30**) was synthesized by the condensation of octahydropyrazinopyridoindole with γ-chloropropyl 4-fluorophenyl sulphone (**29**). The latter (**29**) was obtained from the corresponding amino compound (**26**) by diazotization with sodium nitrite in fluoroboric acid, followed by thermal decomposition of the salt (**28**) thus formed.

*Pharmacological Activity*

The compounds **6-9** and **19-24** were tested for their acute toxicity, gross observational effects reduction in spontaneous and forced locomotor activities, and electroshock seizures in mice at 0.2 $LD_{50}$ dose by standard methods as described in our earlier papers[1,5]. These compounds were also tested for their diuretic (chlorothiazide as standard), prevention of passive cutaneous anaphylaxis (PCA) and antiinflammatory activity against carageenan induced oedema in male mice at 0.2 $LD_{50}$ dose, while other compounds were tested at fixed doses, i.e. at 60 mg/kg for antiinflammatory, 30 mg/kg diuretic (Furosemide as standard) and 10 mg/kg i.p. for CNS activities like antiacetylcholine, antiadrenaline, antihistamine, analgesic, antireserpine and antiisoprenaline. All these compounds were tested for their effect on blood pressure and respiration in anaesthesized cats by administering different doses. The significant results are summarised in Table 2. These compounds exhibited a number of activities such as diuretic (**8-11**, **13**, **20** and **23**), PCA (**9** and **22**), antiinflammatory (**10-13**, **20** and **23**) and anxiolytic (**27** and **30**).

Among the compounds which had variations at 1-position of propane by different heterocyclics containing benzylpiperidine and piperazine in open or in rigid conformation, and had arylthio or arylsulphono group at 3-position, 1-(4-benzylpiperidin-1-yl)-3-(4-acetamidophenylthio)propane (**7**) and 1-(1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-2-yl)-3-(4-acetamidophenylthio]propane (**8**) showed promising activity in the preliminary

Table 2—Pharmacological Activities of Compounds

| Compd | CVS activity[a] in mg/kg i.v. | | | | | | Other activities[b] and toxicity |
|---|---|---|---|---|---|---|---|
| | 1 mg | | 2.5 mg | | 5 mg | | |
| | Fall in B.P. (mm) | Duration (min) | Fall in B.P. (mm) | Duration (min) | Fall in B.P. (mm) | Duration (min) | |
| **6** | 20 | 9.5 | 26 | 20 | 38 | 24 | $ALD_{50}$[c] = 147 |
| **7** | 37 | 56 | 42 | 77 | 92 | 70 | $ALD_{50}$ = 147, Adr. reversal[d] |
| **8** | 53 | 36 | 84 | 113 | 52 | 110 | Diuretic[e] 106(13); $ALD_{50}$ = 68.1 |
| **9** | 14 | Tr | 16 | Tr | 24 | 20 | Diuretic 62(200); PCA[f] 63(200); $ALD_{50}$ > 1000 |
| **10** | No effect | | No effect | | No effect | | AI[g] 44(60); Diuretic 48(30) |
| **11** | 28 | 13 | No effect | | No effect | | AI 25(60); Diuretic 40(30) |
| **12** | No effect | | 24 | 24 | No effect | | AI 10(30) |
| **13** | No effect | | — | — | No effect | | AI 11(30); Diuretic 18(30) |
| **14** | 10 | Tr | 16 | Tr | No effect | | |
| **15** | 20 | 7 | 24 | Tr | — | — | |
| **16** | 44 | 3 | 56 | 58 | 102 | 75 | |
| **17** | No effect | | No effect | | No effect | | |
| **19** | No effect | | 14 | Tr | 20 | Tr | $ALD_{50}$ = 681 |
| **20** | 28 | H | 34 | 16 | — | — | AI 55(63); Diuretic 46(63); $ALD_{50}$ = 316 |
| **21** | 33 | 24 | 54 | 38 | 44 | 22 | $ALD_{50}$ = 1000 |
| **22** | 20 | 3 | 24 | Tr | 34 | 8 | PCA 42(63); $ALD_{50}$ = 316 |
| **23** | 26 | 3 | 36 | 8 | 46 | 10 | AI 64(43); Diuretic 34(43); $ALD_{50}$ = 215 |
| **24** | 45 | 88 | 62 | 50 | 48 | 52 | Adr. reversal; $ALD_{50}$ = 1000 |
| **25** | 32 | Tr | — | — | 24 | 24 | |
| **27** | — | — | — | — | — | — | CAR[h] 20(10) |
| **30** | — | — | — | — | — | — | CAR 20(10) |

[a]Fall in blood pressure in mm of Hg; Tr = transient.
[b]Figures in paranthesis indicate dose in mg/kg.
[c]Approximate $LD_{50}$ mg/kg i.p. (mice).
[d]Adrenaline reversal.
[e]Diuretic activity (oral), figures in parantheses describe dose in mg/kg.
[f]PCA for prevention of passive cutaneous anaphylaxis activity, figures in parantheses describe dose in mg/kg.
[g]Antiinflammatory activity against carageenan-induced oedema in mice.
[h]% conditioned avoidance response in rats. Figures in parentheses describe dose in mg/kg.

testing. These were studied in greater detail, where **7** showed adrenaline reversal at 5 mg/kg dose but was less effective than **8**, which lowered the blood pressure by 35 mm of Hg even at 0.5 mg/kg dose for 44 min. Substitution by other groups such as methoxy (**10**), methyl (**12**), amino (**16**) or dimethylamino (**25**) in the phenyl ring of the arylthio residue of **8**, and replacement of S by $SO_2$ group (**21**) were studied. It was found that compounds **10** and **12** had almost no effect on blood pressure, while **25** exhibited a very weak hypotensive activity. Compounds **16** and **20** showed hypotensive activity; the former was better than the latter but was less effective than **8**. The compounds **27** and **30**, particularly the latter are the analogues of centbutindole[12], a neuroleptic under clinical trials, where the C=O group has been replaced by the $SO_2$ group. These compounds showed weak CNS depressant activity (anxiolytic) as compared to centbutindole as evidenced by conditioned avoidance response (CAR) test in rats at 10 mg/kg i.p. dose in rats carried out by the method of Cook and Weidley[13].

## Experimental Procedures

All compounds were routinely checked for their structures by IR spectra on a Perkin-Elmer 157 infrared spectrophotometer ($\nu_{max}$ in $cm^{-1}$), PMR spectra recorded on Perkin-Elmer R-32 (90 MHz) and El-360 (60 MHz) spectrophotometers (chemical shifts in δ-scale) using TMS as internal reference, and mass spectra recorded on a Jeol JMS D-300 instrument. Melting points were taken in an electrically heated apparatus and are uncorrected. All the compounds were analysed for carbon, hydrogen, nitrogen and the results were within ± 0.4% of the calculated values.

### γ-*Chloropropyl*-4-*acetamidophenyl sulphide* (**3**)

1-Bromo-3-chloropropane (**1**; 0.952 g, 6.0 mmol) was added to a stirred solution of NaOH (0.24 g, 6.0 mmol) in minimum amount of water,

ethanol (15 ml) and *p*-acetamidothiophenol (1.0 g, 6.0 mmol). The reaction mixture was stirred at 100° for 2 hr and concentrated to give **3** which crystallised from ether-hexane, yield 0.7 g (50%), m.p. 69-70°; IR(KBr): 3300, 1680, 1600, 1500, 1400, 1320, 1260, 1100, 1020, 840, 760; PMR($CCl_4$): 1.7-2.2 (*m*, 2H, $CH_2$), 2.0 (*s*, 3H, $CH_3$), 2.8 (*t*, 2H, $S-CH_2$), 3.5 (*t*, 2H, $Cl-CH_2$), 7.5-7.0 (*dd*, 4H, Ar − *H*); MS: *m/z* 244 ($M^{+\cdot}$).

Similarly, compounds **4** and **5** were prepared from the corresponding thiophenols. Their characterization data are given below:

γ-*Chloropropyl* 4-*methoxyphenyl sulphide* (**4**)

Oil, yield 57%; IR(neat): 3000, 1600, 1500, 1470, 1445, 1300, 1250, 1180, 1010, 1040, 840; PMR($CCl_4$): 1.7-2.3 (*m*, 2H, $CH_2$), 2.8 (*t*, 2H, $CH_2Cl$), 3.5 (*t*, 2H, $S-CH_2$), 3.65 (*s*, 3H, $OCH_3$), 6.65 (*d*, 2H, Ar − *H*, *o* to S), 7.2 (*d*, 2H, Ar − *H*, *o* to $OCH_3$): MS: *m/z* 216 ($M^{+\cdot}$).

γ-*Chloropropyl* 4-*methylphenyl sulphide* (**5**)

Oil, yield 65% IR(neat): 2900, 1500, 1440, 1300, 1290, 1220, 1100, 1020, 960, 820; PMR($CCl_4$): 1.7-2.3 (*m*, 2H, $CH_2$), 2.2 (*s*, 3H, $CH_3$), 2.8 (*t*, 2H, $CH_2Cl$), 3.5 (*t*, 2H, $SCH_2$), 6.8-7.2 (*m*, 4H, Ar − *H*); MS: *m/z* 200 ($M^{+\cdot}$).

1-(4-*Benzylpiperazin*-1-*yl*)-3-4-*acetamidophenylthio*)*propane* (**6**)

A mixture of 1-benzylpiperazine (0.775 g; 4.4 mmol) compound **3** (1.217 g; 4.9 mmol), $Na_2CO_3$ (0.23 g; 2.2 mmol) and NaI (0.12 g; 8.0 mmol) in dry DMF (10 ml) was stirred at 80° for 20 hr, cooled and poured into water (30 ml). The separated solid was filtered, washed with water and crystallized from benzene-hexane to give **6** (Table 1); IR(KBr): 3400-2800, 1600, 1520, 1490, 1400, 1370, 1310, 1290, 1260, 1150, 1130, 1000, 810, 750, 700; PMR($CDCl_3$): 2.35 (*s*, 3H, $NHCOCH_3$), 2.7 (*t*, 2H, $SCH_2$), 3.4 (*s*, 2H, $NCH_2$), 1.3-2.5 (*m*, 12H, aliphatic-*H*), 7.2-7.5 (*m*, 9H, Ar − *H*), MS: *m/z* 383 ($M^{+\cdot}$).

Under similar reaction conditions compounds **19-21**, **27** and **30** were prepared. Their characterization data are given in Table 1.

1-(4-*Benzylpiperazin*-1-*yl*)-3-(4-*aminophenylthio*)-*propane* (**14**)

Compound **6** (0.50 g; 1.5 mol) in HCl (15%, 15 ml) was refluxed at 130° for 2 hr. The reaction mixture was cooled, basified with ammonia and extracted with chloroform (2 × 50 ml). The chloroform extract was dried (anhyd. $Na_2SO_4$) and concentrated to give **14** as an oil; IR(neat): 3400, 3000, 2700, 1640, 1620, 1500, 1460, 1300, 1180, 1140, 1020, 840, 760, 720; MS: *m/z* 341 ($M^{+\cdot}$); PMR($CDCl_3$): 2.7 (*t*, 2H, $SCH_3$), 3.4 (*s*, 2H, $N-CH_2$), 1.3-2.5 (*m*, 12H, aliphatic-H), 6.5 (*d*, 2H, Ar − *H*, *o* to $NH_2$), 7.2 (*d*, 2H, Ar − *H*, *o* to S), 7.1 (*bs*, 5H, Ar − *H*); MS of 14 HCl: *m/z* 377 ($M^{+\cdot}$).

Similarly other compounds **15-17**, **22-24**(Table 1) and **26** were prepared.

γ-*Chloropropyl* 4-*aminophenyl sulphone* (**26**)

It crystallized from ethanol, yield 55%, m.p. 92°; IR(KBr): 3400, 3200, 1640, 1600, 1500, 1400, 1140, 1100, 1200, 1150, 1100, 1040, 900, 840, 790, 640; PMR($CDCl_3$): 1.8-2.3 (*m*, 2H, $CH_2$), 3.1 (*t*, 2H, $ClCH_2$), 3.5 (*t*, 2H, $SCH_2$), 4.2 (*s*, 2H, $NH_2$), 6.6 (*d*, 2H, Ar − *H*, *o* to $NH_2$), 7.5 (*t*, 2H, Ar − *H*, *o* to $SO_2$).

γ-*Chloropropyl* 4-*acetamidophenyl sulphone* (**18**)

To a solution of **3** (0.20 g; 0.82 mmol) in acetic acid (1.6 ml) and water (0.4 ml) was added $KMnO_4$ (0.20 g; 1.2 mmol) in small portions. The reaction mixture was stirred at 30° for 4 hr, and decomposed with $H_2O_2$ solution (3 ml). The separated solid was filtered, washed, dried and crystallised from methanol to give **18**, yield 0.190 g (90%), m.p. 178-79°; IR(KBr): 3250, 1680, 1600, 1540, 1500, 1400, 1380, 1300, 1260, 1200, 1140, 1100, 1020, 990, 900, 860, 800, 660; PMR($CDCl_3$ + DMSO-$d_6$): 1.9-2.3 (*m*, 2H, $CH_2$), 2.15 (*s*, 3H, $CH_3$), 3.2 (*t*, 2H, $SCH_2$), 3.6 (*t*, 2H, $ClCH_2$), 7.8-7.6 (*m*, 4H, Ar − *H*); MS: *m/z* 275.

1-(1,3,4,6,11,11*a*-*Hexahydro*-2*H*-*pyrazino*[1,2-*b*]-*isoquinolin*-2-*yl*)-3-(4-*dimethylaminophenylsulphono*)*propane* (**25**)

A solution of 1-(1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-2-yl)-3-(4-aminophenylsulphono)propane (**4**, 0.60 g, 1.4 mmol) and formaldehyde (37% solution, 1 ml) in ethanol (20 ml) containing Pd/C (10%, 0.05 g) was shaken in paar apparatus at 50 psi under hydrogen atmosphere for 72 hr at 30°. The reaction mixture was filtered, the filtrate concentrated and crystallized from ethanol to give **25** (Table 1); IR(KBr): 3900, 2900, 1600, 1460, 1400, 1300, 1140, 1100, 1000, 840, 800, 760, 700; PMR($CDCl_3$ + DMSO-$d_6$): 3.0 [*s*, 6H, $N(CH_3)_2$], 1.5-3.7 (*m*, 17H, aliphatic-*H*), 6.75 [*d*, 2H, Ar − *H*, *o* to $N(CH_3)_2$], 7.65 (*d*, 2H, Ar − *H*, *o* to $SO_2$), 7.0 (*bs*, 4H, rest Ar − *H*); MS: *m/z* 413 ($M^{+\cdot}$).

γ-*Chloropropyl* 4-*fluorophenyl sulphone* (**29**)

Fluoroboric acid (35%, 3 ml) was added to a stirred solution of γ-chloropropyl 4-aminophenyl

sulphone (**2**; 0.55 g, 3.5 mmol) in THF (6 ml). The reaction mixture was cooled (5°C) and a saturated aq. solution of $NaNO_2$ (0.2 g, 2.89 mmol) added to it dropwise. The separated solid was filtered after 10 min of stirring. It was washed with fluoroboric acid (2%, 10 ml), methanol (10 ml) and ether (10 ml) to give the diazonium salt (**28**). This salt was used as such in the next step.

The diazonium salt was decomposed by heating at 115-30° and the resulting fluoro derivative (**29**) purified by column chromatography, yield .300 g (53.9%); IR(neat): 3400, 3000, 1600, 1500, 1400, 1320, 1300, 1220, 1150, 1095, 840, 760, 690; PMR($CDCl_3$): 2.05-2.45 (*m*, 2H, $CH_2$), 3.2 (*t*, 2H, $SO_2CH_2$), 3.55 (*t*, 2H, $CH_2Cl$), 7.5-7.35 (*m*, 2H, Ar – *H*, *o* to F), 7.7-8.0 (*m*, 2H, Ar – *H*, *o* to $SO_2$).

**Acknowledgement**

We are thankful to Mr Zahid Ali for excellent technical assistance. One of us (J R) is thankful to the Director, CDRI for the award of a research fellowship.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 766-767

## *Notes*

# Synthesis of Linearly Fused 2,8-Dialkyl-4,6-dioxo-4*H*,6*H*-benzo[1,2-*b*:5,4-*b*′]dipyrans

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*Received* 29 *July* 1986; *accepted* 17 *November* 1986

2,8-Diethyl/dipropyl-4,6-dioxo-4*H*,6*H*-benzo[1,2-*b*:5,4-b′]-dipyran (IVa,b) have been prepared by Claisen condensation of 5-acetyl-2,4-dihydroxyacetophenone (I) with ethyl butyrate and ethyl propionate respectively followed by acid-catalysed cyclization of the resulting diketone (IIIa,b) with conc HCl. Claisen condensation of 2,4-dihydroxy-5-propionylpropiophenone (V) with ethyl butyrate and ethyl propionate furnishes 2,8-dipropyl-(VIa)- and 2,8-diethyl-(VIb)-3,7-dimethyl-4,6-dioxo-4*H*,6*H*-benzo [1,2-*b*:5,4-*b*′]dipyrans respectively.

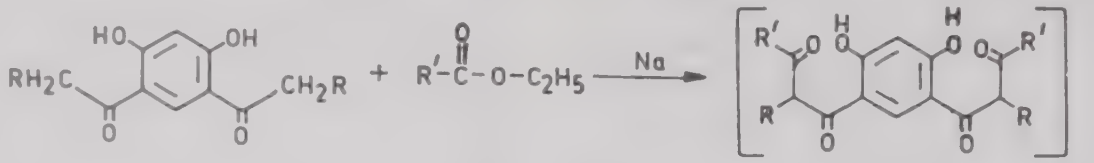
Several linearly and angularly fused benzo-γ-dipyrones possess antiallergic activity[1] comparable to that of marketed drug disodium chromoglycate[2]. The linearly fused benzo-γ-dipyrones are several times more active than the angularly fused ones[1,3]. The title investigation is an extension of our earlier work[3] on linearly fused benzo-γ-dipyrones.

Our approach towards the synthesis of benzo-γ-dipyrones (IVa,b) involved initial condensation of 5-acetyl-2,4-dihydroxyacetophenone (I)[4] with ethyl butyrate (IIa) (in excess) in the presence of sodium methoxide under Claisen condensation reaction conditions. The resulting yellow diketone (IIIa), without isolation, was cyclised using conc hydrochloric acid to yield 2,8-dipropyl-4,6-dioxo-4*H*,6*H*-benzo[1,2-*b*;5,4-*b*′]dipyran (IVa). Likewise, condensation of I with ethyl propionate (IIb) followed by acid-catalysed cyclisation of crude IIIb furnished IVb. For the synthesis of VIa,b 2,4-dihydroxy-5-propionylpropiophenone (V)[5] was condensed, separately with ethyl butyrate (IIa) and ethyl propionate (IIb) to yield the respective diketones IIIc and IIId which on acid catalysed cyclisation gave the corresponding 2,8-dipropyl-(VIa)- and 2,8-diethyl-(VIb)-3,7-dimethyl-4,6-dioxo-4*H*, 6*H*-benzo [1,2-*b*:5,4-*b*′]dipyrans. Benzo-γ-dipyrones were obtained, albiet in poor yields (12.5%). The compounds (IV and VI) did not show any colouration with alc ferric chloride and were insoluble in aq. NaOH. Further the spectral characteristics of the compounds, given in experimental, support the benzo-γ-dipyrone structure.

2,8-Dipropyl-4,6-dioxo-4*H*,6*H*-benzo[1,2-*b*:5,4-*b*′]dipyran (IVa) was found to have good antiallergic activity (% inhibition of histamine released, 63%) comparable to the activity of disodium chromoglycate (% inhibition of histamine released, 87%) when tested by passive peritoneal anaphylaxis method.[6]

*2,8-Diethyl-4,6-dioxo-4H,6H-benzo[1,2-b:5,4-b′]dipyran (IVb)*

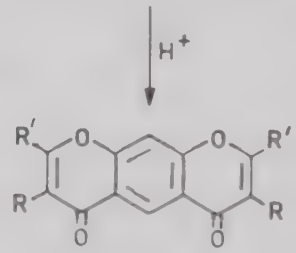
To a mixture of 2,4-dihydroxy-5-acetylacetophenone (I)[4] (1,94 g; 0.01 mol) and ethyl propionate (25




I R=H
V R=CH3

IIa R′=-CH2-CH2-CH3
IIb R′=-CH2-CH3

IIIa R=H; R′=-CH2-CH2-CH3
IIIb R=H; R′=-CH2-CH3
IIIc R=CH3, R′=-CH2-CH2-CH3
IIId R=CH3, R′=-CH2-CH3




IVa R=H; R′=-CH2-CH2-CH3
IVb R=H; R′=-CH2-CH3
VIa R=CH3; R′=-CH2-CH2-CH3
VIb R=CH3; R′=-CH2-CH3

ml), pulverised sodium (1 g) was added with cooling. The reaction mixture was refluxed for 8 hr on a water-bath, cooled to room temperature and excess of sodium destroyed by adding methanol. The reaction mixture was concentrated under reduced pressure and the resulting crude yellow bisdiketone (IIIb) subjected to cyclization by refluxing with conc. hydrochloric acid (10 ml) and glacial acetic acid (25 ml) for 4 hr. Acetic acid was removed under reduced pressure and the resulting residue was poured into cold water (50 ml). The oily substance was extracted with ethyl acetate, the extract dried ($Na_2SO_4$), concentrated and the resulting residue (1.45 g) chromatographed over silica gel (200 mesh, 45 g). Elution with benzene (3 fractions, 200 ml each) yielded the starting I (0.900 g). Subsequent elution with chloroform (5 fractions, 200 ml) yielded IVb which crystallised from benzene as colourless needles (0.25 g); m.p. 140-42°; MS:*m/z* 272 ($M^+$); IR(KBr):1635($cm^{-1}$)(C=O); UV(MeOH):248 (log $\varepsilon$ 4.38), 320 nm(3.92).

Similar condensation of I (1.94 g) with ethyl butyrate (IIa) (25 ml) led to 2,8-dipropyl-4,6-dioxo-4*H*,6*H*-benzo[1,2-*b*:5,4-*b*]dipyran (IVa) which crystallised from benzene as light yellow needles (1 g); m.p. 154-56°; MS: *m/z* 298 ($M^+$); PMR($CDCl_3$, 60 MHz): $\delta$2.68(*t*,*J*=7.5Hz, 4H), 1.86 (*sextet*, *J*=7.5Hz and 8.0Hz, 4H), 1.07 (*t*,*J*=8.0 Hz,6H), 7.5(*s*,$C_{10}$-H), 8.5 (*s*,$C_5$-H), 6.24 (*s*,2H, $C_3$-H and $C_7$-H); IR(KBr) 1640 $cm^{-1}$ (C=O); UV (MeOH):251 (log $\varepsilon$ 4.36), 337 nm (4.12).

Likewise, V (2.22 g) and IIa (25 ml) furnished VIa which crystallised from benzene as light yellow flakes (0.6 g); m.p. 163-64°; MS:*m/z* 326($M^+$); IR(KBr):1635 $cm^{-1}$ (C=O); UV(MeOH):256 (log $\varepsilon$ 4.48), 319 nm(3.76).

Condensation of V with IIb furnished VIb which crystallised from benzene-petroleum ether as colourless needles (0.5 g); m.p. 146°; MS:*m/z* 298($M^+$); IR(KBr) 1640 $cm^{-1}$ (C=O); UV(MeOH):252 (log $\varepsilon$ 4.40), 340 nm(4.15). All the compounds gave satisfactory analytical data.

The authors express their thanks to Dr M B Bhide, Asst Director and Professor of Pharmacology, Haffkine Institute, Bombay for screening antiallergic activity. One of us (KCP) thanks UGC, New Delhi for a junior research fellowship.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 768-769

# Synthesis of 4-(β-Iodoethyl)-7-isopropyl-8-methoxyisochroman-3-one†

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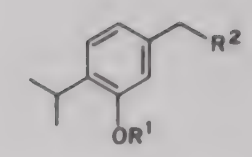
*Received* 29 *September* 1986; *accepted* 4 *December* 1986

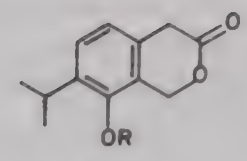
4-(β-Iodoethyl)-7-isopropyl-8-methoxyisochroman-3-one (**13**) has been synthesised from 3-hydroxy-4-isopropylbenzyl alcohol (**1**) in overall good yield.

Polycyclic systems containing atleast one aromatic ring are conveniently prepared by stereoselective intramolecular trapping of the *o*-quinodimethanes[1]. Oppolzer[2] has indicated the utility of isochroman-3-one for the generation of *o*-quinodimethanes. We thought that a suitably substituted isochroman-3-one such as **13** can be a good intermediate for the synthesis of isodehydroabietenolide[3] and related polycyclic natural products. Herein we describe a practical synthesis of the title isochromanone (**13**).

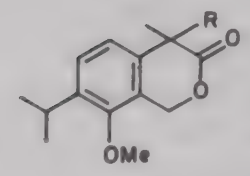
3-Hydroxy-4-isopropylbenzyl alcohol[6] (**1**) on selective acetylation gave a mixture of the monoacetate (**2**) and diacetate (**3**) in 6:1 ratio, **2** being obtained as the major product (60%). **2** on treatment with thionyl chloride gave the chloride (**4**), which when treated with KCN in DMSO furnished the nitrile (**6**). Alternatively **1** was converted into the benzyl iodide (**5**) in quantitative yield with trimethylsilyl iodide[7]. The iodide (**5**) on treatment with KCN in DMSO gave the nitrile (**6**). Hydrolysis of **6** with ethanolic KOH led to the acid (**7**), which on hydroxymethylation[8] with benzeneboronic acid and paraformaldehyde followed by $H_2O_2$ decomposition furnished 8-hydroxy-7-isopropylisochroman-3-one (**8**). Compound **8** on methylation gave the methyl ether (**9**). Base-catalysed alkylation (NaH) of **9** with THP ether of ethylene bromohydrin and methyl iodide followed by acid hydrolysis of THP ether (**11**) gave the dialkylated products **12** and **10**. The alcohol **12** on treatment with trimethylsilyl iodide gave the desired isochroman-3-one (**13**) in good yield.



**1** $R^1$=H, $R^2$=OH
**2** $R^1$=Ac, $R^2$=OH
**3** $R^1$=Ac, $R^2$=OAc
**4** $R^1$=Ac, $R^2$=Cl
**5** $R^1$=H, $R^2$=I
**6** $R^1$=H, $R^2$=CN
**7** $R^1$=H, $R^2$=$CO_2H$



**8** R=H
**9** R=Me



**10** R=Me
**11** R=$CH_2CH_2OTHP$
**12** R=$CH_2CH_2OH$
**13** R=$CH_2CH_2I$

*3-Acetoxy-4-isopropylbenzyl alcohol* (**2**)

To a cooled (0°C) solution of **1** (8.3 g, 50 mmol) in KOH (10%, 2.8 g, 50 mmol), acetic anhydride (8.1 g, 75 mmol) was added dropwise during 30 min. The reaction mixture was stirred for 3 hr at room temperature. Erective work-up and washing with dil. NaOH gave 7.5 g of a neutral fraction. Alkaline solution on neutralization with dil. HCl gave 2 g of the starting **1**. The neutral portion on column chromatography (florisil; pet. ether-ethyl acetate, 8:2) gave the diacetate **3** (1.25 g, 10%) and the desired monoacetate **2** (6.24 g, 60%) as thick liquid. Monoacetate **2**: IR (neat): 1750, 3250 $cm^{-1}$; PMR ($CCl_4$): δ 1.2 (6H, *d*), 2.2 (3H, *s*), 2.6 (1H, *s*), 2.6-3.2 (1H, *m*), 4.4 (2H, s), 6.8-7.1 (3H, *m*); MS: *m/z* 208 ($M^+$).

*3-Hydroxy-4-isopropylbenzyl cyanide* (**6**)

Method A: To a mixture of **2** (4.16 g, 20 mmol), pyridine (3 drops) and dry benzene (20 ml), a solution of thionyl chloride (7.15 g, 60 mmol) in dry benzene (10 ml) was added during 30 min. The mixture was stirred for 3 hr and benzene was removed under reduced pressure. Usual work-up gave the bnenzyl chloride **4** (4.03 g, 93%) as pale yellow oil, which was as such immediately used for the next step. **4** (4 g, 17.6 mmol) in DMSO (40 ml) was treated with KCN (3 g) and the reaction mixture stirred overnight at room temperature. Dilution with water and extractive work-up afforded a crude product (3 g), which crystallized from ether-pet. ether (1:2) to give **6** (2.8 g, 90%); m.p. 70-72°C; IR (KBr): 2260, 3400 $cm^{-1}$; PMR ($CDCl_3$): δ 1.7 (6H, *d*), 3.6 (1H *m*), 4.1 (2H, *s*), 6.5 (1H, *bs*), 7.1-7.5 (3H, *m*); MS: *m/z* 175 ($M^+$), 160 ($M-CH_3$), 149 (M-CN).

Method B: To a mixture of **1** (3.22 g, 20 mmol), sodium iodide (6g, 40 mmol) and dry acetonitrile (100 ml), a solution of trimethylsilyl chloride (5.4 g, 50 mmol) in acetonitrile (60 ml) was added at 10° under nitrogen atmosphere. The reaction mixture was allowed to warm-up to room temperature during 30 min. Extractive work-up gave the unstable benzyl io-

†NCL Communication No. 4101

dide **5** (5.5 g, 90%), which (4.4 g) was dissolved in DMSO and treated with KCN (2.8, 50 mmol) and the reaction mixture stirred overnight at room temperature. Dilution with water followed by usual work-up gave a crude product (3.5 g), which crystallized from pet. ether-ether (2:1) to afford **6** (3.2 g, 92%) as white plates, m.p. and m.m.p. 70-72°.

3-*Hydroxy*-4-*isopropylphenyl acetic acid* (**7**)

A mixture of **6** (2.1 g, 12 mmol), KOH (3.2 g, 30 mmol) and ethanol (30 ml) was refluxed for 24 hr. Work-up as usual afforded the acid (**7**) (2.16 g), which crystallized from pet. ether-dichloromethane (3:2) to give pure acid **7** (1.9 g, 82%) as needles, m.p. 98-100°; IR ($CHCl_3$): 1680, 3430 $cm^{-1}$; PMR ($CDCl_3$): δ 1.4 (6H, *d*), 3.4 (1H, *m*), 3.8 (2H, *s*), 6.9 (1H, *s*), 7.0-7.5 (3H, *m*), 8.0 (1H, *s*); MS: *m/z* 194 ($M^+$) (Found: C, 67.8; H, 7.1. $C_{11}H_{14}O_3$ requires C, 68.1; H, 7.2%).

8-*Hydroxy*-7-*isopropylisochroman*-3-*one* (**8**)

A mixture of **7** (2.9 g, 15 mmol), benzeneboronic acid (2.2 g, 18 mmol), propionic acid (0.5) and benzene (75 ml) was heated under reflux for 1.5 hr using Dean-Stark apparatus. Paraformaldehyde (3.53 ) was added to the refluxing reaction mixture in portions (every 2 hr) during 12 hr. The benzene was removed under reduced pressure and residue taken up in THF (50 ml). To this was added $H_2O_2$ (5 ml, 30%) and stirred for 2 hr at 10-15°. The dil. HCl (19 ml, 2 *N*) was added and stirred for 15 min. THF was removed under reduced pressure and extractive work-up gave 2.6 g of the crude **8** which crystallized from dichloromethane-pet. ether (1:2) to give pure lactone **8** (2.52 g, 75%) as white plates, m.p. 125-26°; IR ($CHCl_3$): 1740, 3600 $cm^{-1}$; PMR ($CDCl_3$): δ 1.27 (6H, *d*), 3.15 (1H, *m*), 3.65 (2H, *s*), 5.5 (2H, *s*), 5.7 (1H, *s*), 6.8 (1H, *d*, $J$ = 8.5 Hz), 7.2 (1H, *d*, $J$ = 8.5 Hz); MS: *m/z* 206 ($M^+$) Found: C, 70.4; H, 6.6. $C_{12}H_{14}O_3$ requires C, 70.0; H, 6.8%).

7-*Isopropyl*-8-*methoxyisochroman*-3-*one* (**9**)

A mixture of **8** (2.06 g, 10 mmol), dimethyl sulphate (1 ml), anhyd. $K_2CO_3$ (2 g) and dry acetone (30 ml) was refluxed for 6 hr (TLC monitoring). It was cooled, filtered, acetone removed and the residue crystallized from dichloromethane-pet. ether (1:2) to give **9** (2.15 g, 97.5%) as white plates, m.p. 79-80°; IR ($CHCl_3$): 1670 $cm^{-1}$; PMR ($CDCl_3$): δ 1.25 (6H, *d*), 3.35 (1H, *m*), 3.70 (2H, *s*), 3.8 (3H, *s*), 5.5 (2H, *s*), 7.1 (1H, *d*, $J$ = 8.5 Hz), 7.4 (1H, *d*, $J$ = 8.5 Hz); MS: *m/z* 220 ($M^+$) (Found: C, 71.1; H, 7.3. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%).

*Alkylation of* **9**

To a solution of **9** (1.1 g, 5 mmol) in HMPA-THF (1:1, 10 ml), sodium hydride (0.15 g, 6 mmol) was added at 0°C under $N_2$ atmosphere and stirred for 30 min. To this was added THP ether of ethylene bromohydrin (1.5 g, 5 mmol) with stirring. The reaction mixture was stirred at room temperature for 2 hr, cooled to 0°C and NaH (0.15 g, 6 mmol) added and stirred for 30 min. Methyl iodide (1.42 g, 10 mmol) was added, reaction mixture stirred at room temperature for 2 hr and treated with cold water. Extractive work-up gave the THP ether **11**. The THP ether **11** was deprotected by treating it with 2 *N* HCl in THF (20 ml). The alkylated product was separated by column chromatography (florisil; pet. ether-ethyl acetate, 5:1) to give 7-isopropyl-8-methoxy-4-methyl-4-(β-hydroxyethyl)isochroman-3-one (**12**, 0.7 g, 50%) as a thick oil, 4,4-dimethyl-7-isopropyl-8-methoxy isochroman-3-one (**10**, 0.375 g, 30%) as an oil along with starting **9** (0.11 g, 10%).

Alcohol **12**: IR ($CHCl_3$): 1770, 3350-3450 $cm^{-1}$; PMR ($CDCl_3$): δ 1.25 (6H, *d*), 1.65 (3H, *s*), 2.25 (2H, *m*), 2.7 (1H, *bs*), 3.22-3.65 (3H, *m*), 3.8 (3H, *s*), 5.5 (2H, *s*), 7.1-7.45 (2H, *m*); MS: *m/z* 278 ($M^+$).

Dimethyl compound **10**: IR ($CHCl_3$): 1665 $cm^{-1}$; PMR ($CDCl_3$): δ 1.35 (6H, *d*), 1.7 (6H, *s*), 3.4 (1H, *m*), 3.9 (3H, *s*), 5.7 (2H, *s*), 7.2-7.6 (2H, *m*); MS: *m/z* 248 ($M^+$).

4-(β-*Iodoethyl*)-7-*isopropyl*-8-*methoxy-isochroman*-3-*one* (**13**)

To a solution of **12** (556 mg, 2 mmol) in dry acetonitrile (7 ml), sodium iodide (600 mg, 4 mmol) and trimethylsilyl chloride (1.08 g, 10 mmol) were added at 5-10°C under $N_2$ atmosphere. The reaction mixture was warmed to room temperature during 1 hr and diluted with water. Extractive work-up and removal of solvent gave a crude product, which was filtered through florisil column (pet ether-ethyl acetate, 5:1) to give **13** (630 mg, 90%) as thick liquid. IR ($CHCl_3$): 1770 $cm^{-1}$; MS: *m/z* 388 ($M^+$), 261 (M-I), 234 (m-I-$C_2H_4$), 205 (M-I-$C_2H_4$-CO).

The authors thank Dr K G Das for helpful discussion and suggestions. One of the authors (MM) is thankful to the CSIR, New Delhi, for the award of a senior research fellowship.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 770-772

# Stereochemical Disposition of Isopropyl Group: Part V — Hydroperoxide Derived from 7-Isopropyl-10-methyl-4-oxobicyclo[4.4.0]dec-5-ene†

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*Received* 16 *June* 1986; *revised and accepted* 22 *December* 1986

The solid α,β-unsaturated ketone (I) on keeping for a few weeks turned into a gummy mass which on crystallisation from aq. ethanol furnished a white crystalline compound characterised as the hydroperoxide (IV) of I. The structure IV has been established by its spectral data and conversion to tertiary alcohol (VI). Some comments have been offered for the stereochemistry of the isopropyl group.

Some time back, we reported[1] the synthesis of epibicyclosesquiphellandrenes via the Wittig reaction of both isomers I (solid) and II (liquid) of the conjugated ketone 7-isopropyl-1-methyl-4-oxobicyclo[4.4.0]dec-5-ene, and revised the stereochemical assignment of the isopropyl group of natural epibicyclosesquiphellandrene as in III. We also commented on the stereochemistry of the isopropyl group of both the isomers (I and II) based on equilibration studies and reported that the signal at δ 0.77 in the PMR spectrum of II was in fact due to one of the methyl groups of the isopropyl moiety because of shielding effect of the enone double bond.

The solid ketone (I) on keeping for a few weeks turned into a gummy mass which on crystallisation from aq. ethanol furnished the hydroperoxide as a white crystalline solid, m.p. 134-35°. It was analysed for $C_{14}H_{22}O_3$; *m/z* 238 ($M^+$); IR (film): 3331 (O−OH), 1667, 1639 $cm^{-1}$ (conj. )C=O); PMR ($CDCl_3$): δ 0.90 and 1.0 [2*d*, 8H, $-CH(CH_3)_2$, $J=7$ Hz], 5.86 (*s*, 1H, $C_5$-H); UV(MeOH): 240 nm; $[\alpha]_D^{26}$ + 32.6° ($CHCl_3$).

Two structures IV and V are possible for the hydroperoxide, and for distinction $^{13}C$ NMR study of the compounds I, II, the hydroperoxide, epizonarene (VII) and the ketal (VIII) was undertaken (Table 1). The reasons for including the latter two (VII and VIII) is to pinpoint the C-7 carbon atom. Based on this study structure IV was assigned to the hydroperoxide.

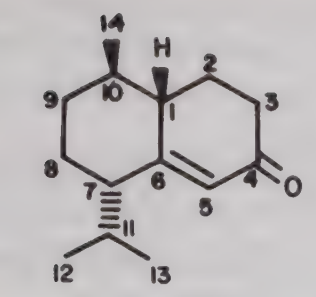
Table 1 — $^{13}C$ NMR Data of I, II, IV, VII and VIII
(calculated values are given in parentheses)

| Carbon No. | (I) | (II) | (IV) | (VII) | (VIII) |
|---|---|---|---|---|---|
| 1 | 46.01 (46.2) | 41.27 (41.0) | 41.34 | 43.35 | 45.43 |
| 2 | 29.18 (29.6) | 28.86* (29.0) | 28.69* | 28.34 | 30.81 |
| 3 | 35.22 (36.6) | 35.74 (36.5) | 35.99 | 31.33 | 23.20 |
| 4 | 199.97 (199.5) | 200.74 (199.3) | 200.46 | 122.96 | 109.96 |
| 5 | 122.05 (124.1) | 125.63 (119.3) | 124.20 | 120.69 | 38.01 |
| 6 | 169.88 (169.5) | 170.24 (169.7) | 163.22 | 135.05 | 136.40 |
| 7 | 51.21 (53.0) | 52.58 (49.5) | 85.77 | 128.10 | 127.60 |
| 8 | 25.48 (30.0) | 25.97 (30.2) | 26.38* | 31.97 | 35.22 |
| 9 | 34.96 (39.9) | 29.96* (28.9) | 27.90* | 28.34 | 30.29 |
| 10 | 39.12 (41.3) | 39.64 (41.1) | 37.87 | 28.34 | 28.99 |
| 11 | 27.04 (33.0) | 27.43 (25.0) | 27.48 | 37.40 | 35.42 |
| 12 | 18.46 (19.9) | 20.74 (21.0) | 16.36 | 20.54 | 20.93 |
| 13 | 20.34 (22.8) | 20.28 (22.8) | 18.66 | 21.06 | 20.73 |
| 14 | 22.03 (22.8) | 21.58 (22.8) | 20.06 | 20.54 | 20.57 |
| 15 | | | | 24.05 | 64.3 |
| 16 | | | | | 64.5 |

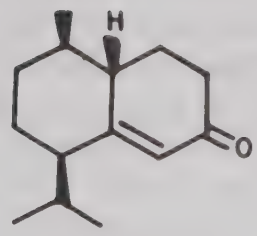
*Assignment can be interchanged.

For convenience, the $^{13}C$ NMR spectrum of the solid ketone (I) was studied first. The signals at δ 199.97, 122.05 and 169.88 could easily be assigned to C-4, C-5 and C-6 respectively. The C-3 being α- to carbonyl group is expected to resonate at a lower field than other methylene carbons in the system and hence its assignment at δ 35.22 was quite reasonable and comparable[2] to a similar carbon in IX. The signal at δ 34.96 was assigned to C-9 as the equatorial methyl at C-10 is known to deshield[3] the adjacent carbon. The C-2 carbon, being adjacent to the ring junction, resonated at lower field than the C-8. Hence, the signals at δ 29.18 and 25.48 were assigned to C-2 and C-8, respectively. Moreover, the chemical shift of C-2 is not expected to vary much from the chemical shift of its counterpart in IX. It is known that an equatorial isopropyl group deshields[4] the α-carbon by about 17 ppm in cyclohexanes which

†NCL Communication No. 4080.




I

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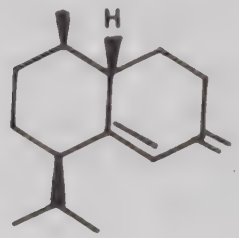


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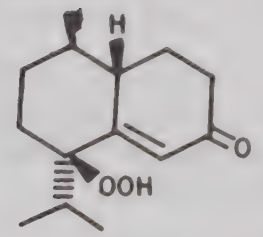
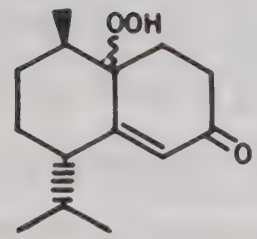
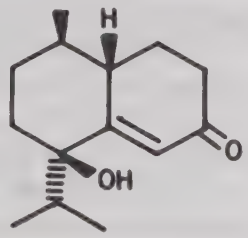



IV




V

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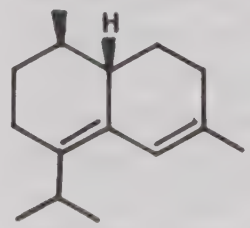


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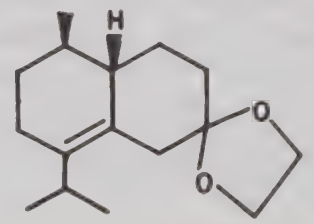
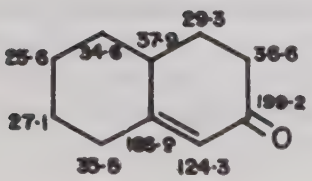



VIII

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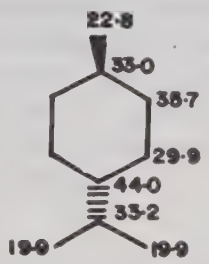
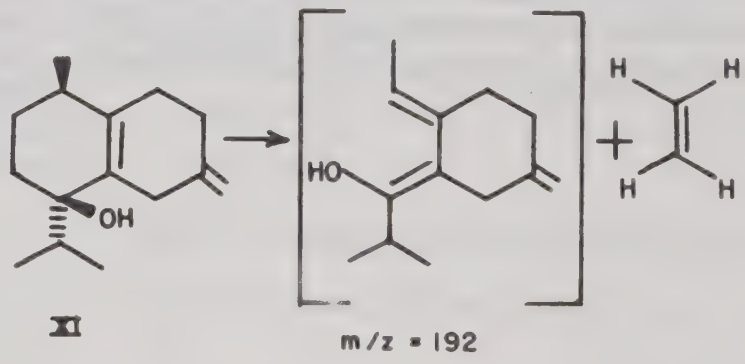



X




XI

is greater than the β-deshielding effect of an equatorial methyl carbon (δ 8.5). The same argument could be extended to the ring system concerned, and hence the signals at δ 51.21 and 46.01 were assigned to C-7 and C-1, respectively. The assignment of the signals at δ 27.01 and 39.12 respectively to C-11 and C-10 was in accordance with the assumption that an isopropyl methine carbon resonates at a higher field compared to the one similar to C-10. These two carbons can be compared to their counterparts in *trans-p*-methane (X)[4,5]. The signal at δ 2.03 was assigned to the equatorial methyl carbon at C-10 in analogy with the methyl carbon in X. The remaining two methyl signals δ 18.46 and 20.34 were due to the isopropyl group (C-12 and C-13).

It is noteworthy to compare the $^{13}C$ chemical shifts of I with those of the isomer II and the peroxide IV. The observed shielding of 4.74 ppm for C-1 and 5.00 ppm for C-9 in II implies that the isomerisation takes place at C-7 because in II, where the isopropyl group is quasi axial, γ-*gauche* interactions between the isopropyl group and the quasi-axial proton at C-1 and axial proton at C-9 lead to increased shielding of C-1 and C-9 eventhough similar isomerisation in cyclohexanes is known to shield the γ-carbon atom by ~ 3.5 ppm[4,5]. The C-7 carbon experiences a downfield shift by 1.37 ppm. This may be attributed to the different ring geometry of the ring system concerned here compared to cyclohexanes. If the isomerisation was at C-10, it would have led to upfield shifts for C-8 and C-2 which were not observed for II.

The hydroperoxide IV also showed appreciable shielding for C-1 and C-9 compared to the solid ketone (I). This could be explained in terms of γ-*gauche* interactions of the hydroperoxy group. If the hydroperoxy group was at C-1, appreciable shielding would have been observed for C-9, C-7 and C-3. Hence, the signal at δ 85.77 was assigned to C-7. Thus, the shielding effects at C-1 and C-9 and the comparison of $^{13}C$ NMR data of IV with those of I and II fully supported the assigned structure IV in the light of chemical evidences (*vide infra*).

The $^{13}C$ chemical shifts of I and II were calculated based on the chemical shifts of 4,4a,5,6,7,8-hexahydro-2(3*H*)naphthalene (IX)[2] using substituent parameters for methyl and isopropyl groups in cyclohexane[4]. These values are given in parentheses in Table 1 and are in fair agreement with the observed values (Table 1).

The structure IV was further confirmed by its PMR spectrum wherein the signals for the isopropyl methyls appeared at δ 0.90 and 1.0 and no signal appeared at 0.77 clearly indicating an α-equatorial nature of the isopropyl group[1]. Further, reduction of IV with triphenylphosphine in hexane[6] gave the tertiary

alcohol (VI), b.p. 180-81° (bath)/1.5 mm; MS: *m/z* 222 ($M^+$) and 204 (M-18); IR: 3413, (−OH), 1672 and 1639 $cm^{-1}$ (conj. $\rangle C=O$): PMR ($CCl_4$): δ 0.90 and 1.0 [*d*, 9H, $-CH(CH_3)_2$ and $C_{10}$-$CH_3$, $J=7$ Hz]. 3.63 (*bs*, 1H, −OH, slowly and partially exchangeable with $D_2O$) and 5.80 (*s*, 1H, $C_5$-H); $[\alpha]_D^{26}$ +28.6° ($CHCl_3$). Again the absence of a signal at 0.77 indicated α-equatorial disposition of the isopropyl group.

Wittig reaction using triphenylphosphonium methylide on IV gave XI instead of the conjugated diene, b.p. 155-56°/2.5 mm; analysed for $C_{15}H_{24}O$; *m/z* 220 ($M^+$); 3521 (−OH), 1650 and 898 $cm^{-1}$ ($=CH_2$): PMR ($CCl_4$): δ 0.90 and 1.0 [2*d*, 9H, $-CH(CH_3)_2$ and $-CH-CH_3$, $J=7$ Hz], 2.26 (*m*, 2H, 5-$CH_2$), 3.46 (*bs*, 1H, O*H*), and 5.03 (*m*, 2H$\rangle C=CH_2$); $[\alpha]_D^{26}$ +11.0° ($CHCl_3$). The base peak in the mass spectrum appeared at *m/z* 192 (M−28) which is due to the loss of ethylene by retro Diels-Alder type of fragmentation. Such fragmentation can be accounted only if the position of the double bond is between C-1 and C-6 and also confirms the position of hydroxy group at C-7.

All the compounds gave satisfactory elemental analyses.

The authors (M V R, A S P and P R R) thank the CSIR, New Delhi for financial support.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 773-775

# Use of Carboxylic Acid—Triphenylprop-2-ynylphosphonium Bromide Adducts for Acylation of Oxygen & Nitrogen Nucleophiles†

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*Received* 13 *October* 1986; *accepted* 9 *December* 1986

Unstable carboxylic acid-triphenylprop-2-ynylphosphonium bromide adducts, i.e. activated vinyl esters (**4**), prepared *in situ* under mild conditions, have been used to acylate the oxygen and nitrogen nucleophiles to give the acylated products (**5**) together with acetonyltriphenylphosphonium bromide (**6**, X = Br). Acetylmethylenetriphenylphosphorane (**7**) is conveniently prepared from **6** by treatment with aq. NaOH at 0°C.

Appleyard and Stirling[1] showed that the benzoate anion could be added to the allenic isomer (**2**)[2] of triphenylprop-2-ynylphosphonium bromide (**1**) and the adduct thus obtained could be used for the acylation of benzylamine. This prompted us to undertake the title investigation.

The carboxylate anions generated *in situ* from the reaction of acids (Table 1) with $NEt_3$ were added to salt (**1**)[2] to afford the adducts (**4**) which were characterized by the characteristic $\nu C=O$ of vinyl esters.

The adducts (**4**) were very sensitive to water and could be easily hydrolysed to ketone (**6**, X = Br) with the liberation of the corresponding acids. For this reason, both the addition as well as the acylation were carried out under strictly anhydrous conditions. The acylations of nucleophiles were performed in $CHCl_3$ solution without isolating the adducts in crystalline forms, if any.

During acylation, the nucleophiles attacked carbonyl carbon of the activated vinyl esters (**4**) forming the acylated products (**5**) (e.g. esters and amides) with the dispalcement of relatively stable enolate anion[1]. The enolate anion abstracted a proton from the system and underwent rapid tautomerization to produce the stable ketone, acetonyltriphenylphosphonium bromide (**6**, X = Br).

It is to be noted that the corresponding triethylprop-2-ynylammonium bromide (**8**)[1], neither underwent isomerization to its allenic isomer in basic media nor gave adduct with an acid and thence amide under identical conditions. This observation indicates that the formation of a stabilized allenic species is necessary for nucleophilic addition. While allenic species is obtainable from **1** having the electron-withdrawing $Ph_3P^+$ at C-1, the same can not be obtained from **8** because of the absence of any such group.

Compounds (**6**) were converted into the stable ylids (**7**)[3] on treatment with aq. NaOH at 0° and again the ylid (**7**) was easily reconverted into its salts (**6**) on treatment with hydrogen halides (LX = Cl, Br, I), and *p*-toluenesulphonic (X = *p*-toluenesulphonate) and picric (X = picrate) acids in methanol medium.

The acylation with adducts (**4**) provides a new approach towards esters and amides, and the adducts (**4**) may act as reagents for acylation of nucleophiles including the carboxyl-protected and amino-protected amino acids or peptides.

*Addition of carboxylic acids to salt* (**1**) *and subsequent acylation of nucleophiles with the adducts: General procedure*

A homogeneous solution of carboxylic acid (0.02 mol) and dry triethylamine (2.0238 g, 0.02 mol) in dry $CHCl_3$ (20 ml) was mixed with salt (**1**) (7.6252 g,

†Part of Ph.D. work of MNI Khandker

Table 1—Characterization Data of Acylated Products (**5**)

| Expt No. | Acid | Nucleophile | Acylated product (**5**) [yield & cryst. solvent[a]] | m.p./b.p. (°) of **5** |
|---|---|---|---|---|
| 1 | Acetic | Methanol | $CH_3COOCH_3$ | Detected by GLC |
| 2 | -do- | Ethanol | $CH_3COOC_2H_5$ | Detected by GLC 120-21° |
| 3 | Phenylacetic | Benzylamine | N-Benzylphenylacetamide (85.33% from B-P) | (lit.[4a] m.p. 122°) |
| 4 | Benzoic | Water | Benzoic acid (77.1% from W) | 120-22° (lit.[4b] m.p. 122°) |
| 5 | -do- | Methanol | Methyl benzoate (79.4%) | 198-203° (lit.[4c] b.p. 199.6°) |
| 6 | -do- | Ethanol | Ethyl benzoate (60.5%) | 211-14° (lit.[4d] b.p. 212.9°) |
| 7 | -do- | Benzylamine | N-Benzylbenzamide (76.19% from B-P) | 104-5° (lit.[4e] m.p. 105-6°) |
| 8 | -do- | *p*-Toluidine | N-*p*-Tolylbenzamide (70.49% from E) | 158-9° (lit.[4f] m.p. 158°) |
| 9 | *p*-Nitro-benzoic | Water | *p*-Nitrobenzoic acid (87.71% from W) | 240° (lit.[4g] m.p. 241.5°) |
| 10 | -do- | Methanol | Methyl *p*-nitrobenzoate (93% from M-W) | 94-96° (lit.[4h] m.p. 96°) |
| 11 | -do- | Ethanol | Ethyl *p*-nitrobenzoate (87.9% from E-W) | 56.5° (lit.[4i] m.p. 57°) |
| 12 | -do- | Benzyl alcohol | Benzyl *p*-nitrobenzoate (95.38% from E-W) | 86-87° (lit.[4j] m.p. 88.5-89°) |
| 13 | Picolinic | *p*-Toluidine | N-*p*-Tolylpicolinamide (75.49% from B-P) | 102-3° (lit.[4k] m.p. 104°) |

[a]B = Benzene; P = petroleum ether (40-60°); W = water; M = methanol; and E = ethanol.

0.02 mol) at room temperature (25-31°) and briskly stirred for 10-20 min with monitoring by IR spectroscopy for νC=O at 1733, 1750 and 1750 $cm^{-1}$ for vinyl benzoate, picolinate and *p*-nitrobenzoate respectively. The nucleophile (amine, 0.02 mol and alcohol, 0.06 mol) in dry $CHCl_3$ (15 ml) was added and the mixture stirred for 20-25 hr at room temperature. After removal of solvent on a boiling water bath, water (70 ml) was added and the cooled mixture (alkaline) extracted with ether (3 × 100 ml) (in the case of $H_2O$ as nucleophile, the ether extract from the previously acidified (aq. HBr) aq. layer was evaporated off and the carboxylic acid characterized by usual methods). The ethereal extract was washed successively with 10% aq. HBr (3 × 125 ml), aq. $NaHCO_3$ (5% w/v) (3 × 125 ml) and water until the extract was free from alkali. The extract was dried ($Na_2SO_4$) and evaporated, and the liquid acylated product obtained was purified by distillation and the solid one by recrystallization. The characterization data of acylated products (**5**) are given in Table 1.

From the filtered aqueous layer, the salt (**6**, X = Br) [m.p. and m.m.p. 223-25° (d) (from MeOH-EtOAc) (Found: C, 63.17; H, 5.06. Calc. for $C_{21}H_{20}BrOP$: C, 63.19; H, 5.05%)] was either isolated as such by extracting with $CHCl_3$ and then crystallizing it from $CHCl_3$-EtOAc in 63-92% yield or converted into the stable ylid (**7**) [m.p. and m.m.p. 204-6° (from MeOH-$H_2O$); lit.[3] 205-6°] in 69-93% yield by treating aq. layer with aq. NaOH (5% w/v) at 0° until just alkaline.

**7** was converted into **6** on reacting with hydrogen halides at room temperature and *p*-toluenesulphonic and picric acids (1 equiv) under reflux for 2 hr in methanol, **6**: X = Cl, yield 87%, m.p. 240° (d) (lit.[3] 237-38°); X = I, yield 68%, m.p. 204-8° (d) (lit.[3] 207-9°); X = *p*-toluenesulphonate, yield 84%, m.p. 163-4° (d) (Found: C, 68.7; H, 5.4. Calc. for $C_{28}H_{27}O_4PS$: C, 68.6; H, 5.5%); IR (KBr): 1720 (νC=O), 1360 ($CH_3$), 1110 (ν Ph-P), 1195 $cm^{-1}$ (ν as $SO_2$); PMR ($CDCl_3$): δ 2.43 (*d*, 3H, $J_{PH}$ = 2 Hz, CO-$CH_3$), 5.53 (*d*, 2H, $J_{PH}$ = 12 Hz, $CH_2$-P), 2.28 (*s*, 3H, $CH_3$), 6.9-8.0 (*m*, 19H, arom) and picrate, yield 57%, m.p. 160-62° (d); IR (KBr): 1715 (νC=O), 1360 ($CH_3$), 1112 $cm^{-1}$ (νPh-P); MS: *m/z* (relative intensity) 318 (26.1), 317 (35.8), 303 (80.6), 277 (35.1), 262 (32.8), 201 (19.4), 183 (100), 165 (27.6), 152 (30.6), 108 (23.1), 107 (35.8), 77 (50.7), 69 (20.1), 57 (29.9), 51 (44.0).

The salts (**6**, X = Cl, I, *p*-toluenesulphonate and picrate) were recrystallized from MeOH-EtOAc-ether and converted into **7** by reacting with aq. NaOH (5% w/v) in water at 0°.

The authors thank Dr M.T.H. Tarafder, Depart-

ment of Chemistry, University of Rajshahi, for the IR specra and the Chittagong University Authority, Bangladesh, for the award of a scholarship to one of them (MNIK).

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 776-778

# Studies on Cepham Analogs: Synthesis, Stereochemistry & Their Conversion into Monocyclic *cis*-β-Lactams

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*Received* 2 *July* 1986; *revised and accepted* 12 *December* 1986

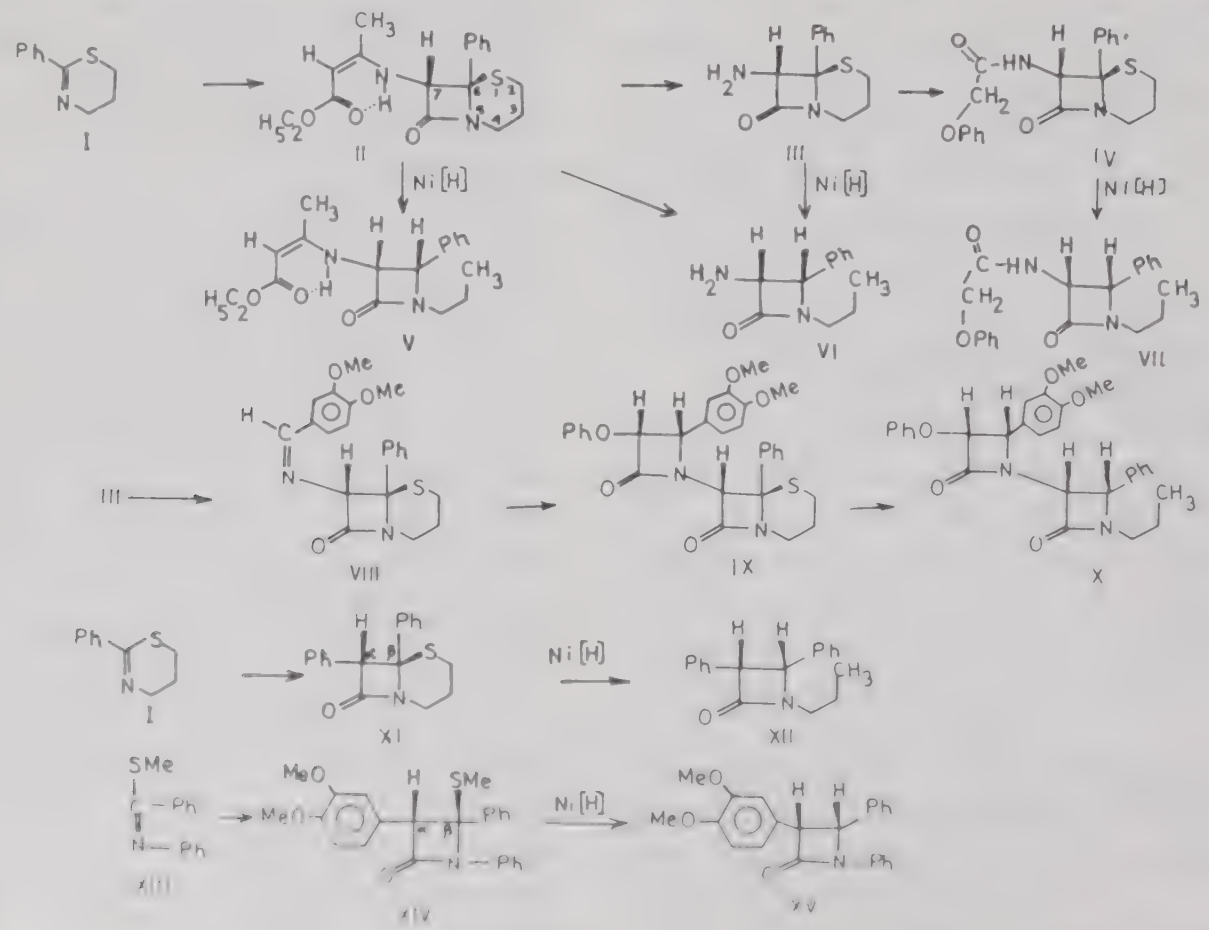
2-Phenyl-5,6-dihydro-4*H*-1,3-thiazine (I) on reaction with potassium carbethoxyacetonylglycinate in the presence of $POCl_3/Et_3N$ in $CH_2Cl_2$ furnishes the 7-enaminocepham (II). The compound I also reacts with phenylacetic acid under similar conditions to provide the 6,7-diphenylcepham (XI). Treatment of II with EtOH/HCl gives the corresponding amine (III) which on acylation with phenoxyacetyl chloride gets converted into the 7-acetamidocepham (IV). The aminocepham (III) also produces the aldimine (VIII) which on acylation with phenoxyacetyl chloride furnishes a novel di-β-lactam (IX). All the cepham analogs (II-IV, IX, XI) are produced as single stereoisomers and have been assigned the *E*-configuration. This is based on their stereospecific conversions into the corresponding monocyclic *cis*-β-lactams (V-VII, X and XII) by Raney-Ni desulphurisation. The directive influence of the sulphur atom of the imines (I and XIII) to orient itself always *cis*- to the $C_\alpha$-H is confirmed in β-lactams (XI and XIV) by their conversion into the corresponding *cis*-β-lactams (XII and XV).

After the discovery[1] that cephalosporin C is a fused dihydrothiazine β-lactam, the synthesis of bicyclic β-lactams became a desirable goal, and efforts in this area resulted in the synthesis of a number of cepham analogs[2-4]. In continuation of our work on the synthesis of β-lactam antibiotics, we report here the preparation, stereochemistry and stereospecific conversion of some cepham analogs to monocyclic *cis*-β-lactams.

We have introduced[5] the use of $POCl_3$ for the construction of a β-lactam ring. By choosing an appropriate acid as well as an imine synthon, several 2-azetidinone derivatives[6-8] were prepared in our laboratory with a view to studying their antibacterial potential. If, in this type of a reaction the imine component is a dihydrothiazine such as I, one can obtain 7-substituted cephams as shown in Scheme 1.

The dihydrothiazine (I) on reaction with potassium carbethoxyacetonylglycinate[9] using $POCl_3/Et_3N$ in $CH_2Cl_2$ yielded the 7-enaminocepham (II) which was converted into 7-amidocepham (IV) via the amine III through the usual reactions. The amine (III) was also converted into the aldimine (VIII) which on subsequent acylation with phenoxylacetyl chloride furnished a novel 7-(2-azetidinyl)cepham (IX) in a fairly good yield. The dihydrothiazine (I) also reacted smoothly with phenylacetic acid to produce 6,7-diphenylcepham (XI).

The formation of these cepham analogs pro-



Scheme 1

ceeded stereoselectively and gave single isomers thereby throwing some light on the reaction mechanism and stereochemistry of the products. One noteworthy observation is the orientation of $C_7$-H with atoms/groups at $C_\beta$-position. The $C_7$-H unmistakably orients itself *cis*- to the $-S-$ atom. Although the PMR spectra of these cephams could not reveal their stereochemistry, yet their *E*-configuration could be ascertained by desulphurisation[10] with Raney Ni. Such reductive desulphurisation has been reported to proceed with the retention of configuration[11]. The Raney-Ni desulphurisation of II-IV, IX and XI led to the corresponding monocyclic β-lactams V-VII, X and XII which were found to have *cis*-orientation as would be expected on the basis of *E*-configuration of these cephams. It is interesting to note that the treatment of II with Raney Ni in acetone for more than 30 min provided directly the amine VI after concomitant removal of the amino-protecting group.

The orientation of $C_\alpha$-H to $-S-$ at $C_\beta$-position in cephams is also true in the case of simple monocyclic β-lactams. Conversion of imine XIII to the β-lactam XIV was also stereoselective, and as expected the Raney-Ni treatment of XIV yielded the *cis*-β-lactam (XV) as shown by its PMR data.

All melting and boiling points reported are uncorrected. IR spectra ($\nu_{max}$ in $cm^{-1}$) were recorded in nujol mull on a Perkin-Elmer model-337 spectrophotometer and PMR spectra in $CDCl_3$ on a Varian EM-390 90 MHz instrument using TMS as internal standard (chemical shifts in δ, ppm). Organic extracts were dried over anhyd. sodium sulphate and the column chromatography was performed over neutral alumina.

*2-Aryl-5,6-dihydro-4H-1,3-thiazine (I)*

A mixture of N-3-hydroxypropylbenzamide (15 g, prepared by the acylation of 3-aminopropanol with benzoyl chloride), $P_2S_5$ (15 g) and benzene (300 ml) was refluxed with constant stirring for 3 hr. The benzene layer was decanted and the white residue treated with a saturated solution of NaOH and extracted with benzene. The extract was washed with brine, dried, solvent removed and the residue distilled to get I in 60% yield, 158-60/10 mm; IR: 1620 (C=N), PMR: 1.85 (*quintet*, 2H, $C_5$-$CH_2$), 3.1 and 3.9 (*t* each, 2H each, ring methylenes), 7.4 and 7.8 (*m* each, 3H and 2H, Ar-*H*) (Found: N, 6.7. $C_{10}H_{11}NS$ requires N, 6.8%).

*7-(1′-Carbethoxy-1′-propen-2′-ylamino)-6-phenylcepham (II)*

A solution of 2-phenyl-5,6-dihydro-4*H*-1,3-thiazine (I, 1.77 g, 0.01 mol), potassium carbethoxyacetonylglycinate (2.25 g; 0.01 mol) and $Et_3N$ (2.52 g; 0.025 mol) was stirred in anhyd. dichloromethane (150 ml) while a solution of $POCl_3$ (1.54 g; 0.01 mol) in dry $CH_2Cl_2$ (50 ml) added to it dropwise at room temperature during 1 hr. After the addition was over, the mixture was stirred for 2 hr and then refluxed for 2 hr. The resulting solution was washed with water and then with brine solution. The organic phase was dried and solvent removed to afford II; IR: 1775 (β-lactam CO) and 1670 (conjugated ester CO); PMR: 1.15 (*t*, 3H, $-COOCH_2CH_3$, $J=7.0$ Hz), 1.85 (*s*, 3H, vinyl $CH_3$), 1.9, 2.75, 3.1 and 4.25 (*m*, each, 2H, 2H, 1H and 1H, ring methylenes), 4.0 (*q*, 2H, $-COOCH_2-$, $J=7.0$ Hz), 4.35 (*s*, 1H, olefinic H), 5.13 (*d*, 1H, $C_7$-H, $J=9.0$ Hz, became a singlet after $D_2O$ exchange), 7.55 (*m*, 5H, Ar-*H*) and 8.62 (*d*, 1H, N-H, $J=9.0$ Hz, exchangeable with $D_2O$).

β-Lactams XI and XIV were prepared by annelating the imines I and XIII with phenylacetic acid and 3,4-dimethoxyphenylacetic acid respectively by the above procedure and recrystallised from EtOH. Their spectral data (IR and PMR) were in complete agreement with their structures. The physical data of II, XI and XIV are given in Table 1.

*7-Phenoxyacetamido-6-phenylcepham (IV)*

Compound II (2.0 g), ethanol (20 ml) and conc. HCl (10 ml) were stirred for 4 hr at room temperature, and the reaction mixture was diluted with water and extracted with dichloromethane (50 ml × 2) to remove any unreacted starting material. The aq. solution was made alkaline with $Na_2CO_3$ (solid) and extracted with dichloromethane (50 ml × 3). The organic layer was washed with water, dried and solvent removed to provide III in 50% yield, m.p. 81-83° (ethanol) (lit.[12] m.p., 81-83°).

Phenoxyacetyl chloride (1.71 g, 0.01 mol) in anhyd. dichloromethane (50 ml) was added dropwise to a well stirred solution of III (2.34 g, 0.01 mol) in dry dichloromethane (100 ml). After the addition was complete, the solution was stirred for another 4-5 at room temperature. The resulting solution was washed with water (50 ml × 2), dried and solvent removed to afford IV in 75% yield, m.p. 151-53° (ethanol) (lit.[12] m.p., 151-53°).

*α-Aldimino-β-lactam (VIII) (Table 1)*

A mixture of III (2.34 g, 0.01 mol) and veratraldehyde (1.66 g, 0.01 mol) in ethanol (50 ml) was refluxed for 5-6 hr on a water-bath, cooled in an ice-bath, and the solid product filtered off under suction, washed with cold ethanol and recrystallized from EtOH to afford VIII; IR: 1765 (β-lactam CO), 1675 (C=N); PMR: 1.9, 2.75, 3.2 and 4.2 (*m* each, 2H,

Table 1—Characterisation Data of the Various Cephams and Monocyclic *cis*-β-Lactams Prepared

| Compd | m.p. °C | Yield (%) | Mol. formula | Found (%) (Calc.) | | |
|---|---|---|---|---|---|---|
| | | | | C | H | N |
| II | 136-38 | 50 | $C_{18}H_{22}N_2O_3S$ | 62.2 (62.4 | 6.3 6.4 | 8.0 8.1) |
| V | Viscous oil | 45 | $C_{18}H_{24}N_2O_3$ | 68.2 (68.4 | 7.4 7.6 | 8.7 8.9) |
| VI | Viscous oil | 45 | $C_{12}H_{16}N_2O$ | 70.4 (70.6 | 7.6 7.8 | 13.6 13.7) |
| VII | 123-25 | 45 | $C_{20}H_{22}N_2O_3$ | 70.9 (71.0 | 6.4 6.5 | 8.1 8.3) |
| VIII | 135-37 | 60 | $C_{21}H_{22}N_2SO_3$ | 65.8 (66.0 | 5.6 5.8 | 7.2 7.3) |
| IX | 182-84 | 60 | $C_{29}H_{28}N_2SO_5$ | 67.3 (67.4 | 5.3 5.4 | 5.2 5.4) |
| X | 110-12 | 45 | $C_{29}H_{30}N_2O_5$ | 71.5 (71.6 | 6.0 6.2 | 5.6 5.8) |
| XI | 143-45 | 60 | $C_{18}H_{17}NOS$ | 73.1 (73.2 | 5.6 5.8 | 4.5 4.7) |
| XII | 296-98 | 35 | $C_{18}H_{19}NO$ | 81.4 (81.5 | 7.1 7.2 | 5.2 5.3) |
| XIV | 155-57 | 60 | $C_{24}H_{23}NSO_3$ | 70.9 (71.1 | 5.6 5.7 | 3.3 3.5) |
| XV | 139-41 | 45 | $C_{23}H_{21}NO_3$ | 76.8 (76.9 | 5.7 5.8 | 3.8 3.9) |

2H and 1H and 1H, ring methylenes), 3.75 and 3.9 (*s* each, 3H each, 2 × $-OCH_3$), 5.18 (*s*, 1H, $C_7$-H), 6.8-7.8 (*m*, 8H, Ar-*H*) and 8.4 (*s*, 1H, aldimine H).

*Di-β-lactam (IX) (Table 1)*

A solution of VIII (3.82 g, 0.01 mol) and triethylamine (1.01 g, 0.01 mol) in $CH_2Cl_2$ (150 ml) was stirred at room temperature while a solution of phenoxyacetyl chloride (1.71 g, 0.01 mol) in $CH_2Cl_2$ (50 ml) added to it dropwise during 30 min. The reaction mixture was stirred overnight at room temperature, refluxed for 1 hr, washed with water and dried. Removal of solvent afforded IX which recrystallised from MeOH; IR: 1775 and 1780 (β-lactam CO); PMR: 1.8, 2.7, 3.2 and 4.1 (*m* each, 2H, 2H, 1H and 1H, ring methylene), 3.8 3.86 (*s* each, 3H each, 2 × $OCH_3$), 4.4 (*d*, 1H, $J$ = 5.0 Hz, $C_4$-H) and 6.0-7.7 (*m*, 13H, Ar-*H*).

*Monocyclic cis-β-lactam (V)*

A solution of II (1.038 g, 0.003 mol) in acetone (50 ml) was stirred and heated under reflux for 1 hr with Raney-Ni (20 g). The catalyst was filtered and washed with acetone. Removal of solvent from the filtrate and recrystallisation of the residue from EtOH gave V (Table 1); IR: 1760 (β-lactam CO) and 1660 (conjugated ester CO); PMR: 0.9 (*t*, 3H, $-CH_2CH_3$), 1.15 (*t*, 3H, ester methyl, $J$ = 7.0 Hz), 1.55 (*m*, 2H, methylene), 1.85 (*s*, 3H, vinyl $-CH_3$), 2.95 and 3.5 (*m* each, 1H each, $-NCH_2$), 4.0 (*q*, 2H, $-COOCH_2$, $J$ = 7.0 Hz), 4.35 (*s*, 1H, olefinic H), 5.05 (*dd*, 1H, $C_3$-H, $J$ = 6.0 and 9.0 Hz), 7.5 (br *s*, 5H, Ar-*H*) and 8.7 (*br*, 1H, N-H, exchangeable with $D_2O$).

The monocyclic *cis*-β-lactams VI, VII, X, XII and XV were prepared by desulphurisation of III, IV, IX, XI and XIV respectively and recrystallised from EtOH. Their physical data are given in Table 1. The IR and PMR spectral data of these lactams agreed well with their structures.

We are thankful to UGC (SAP), New Delhi for financial assistance and the award of senior research fellowship to one of us (VK). We are also thankful to CSIR, New Delhi for the award of a pool officership to UM.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 779-781

# Influence of Substituents on the Synthesis of Thiazolidinones

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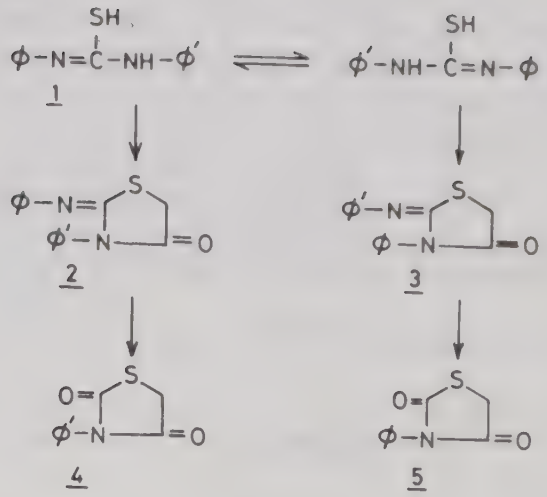
*Received* 15 *April* 1986; *revised and accepted* 22 *December* 1986

The influence of substituents (subunits) in the synthesis of thiazolidinones by the reaction of unsymmetrical thioureas with monochloroacetic acid in ethanol has been rationalised by the characterisaqtion of the hydrolysis products of the resulting thiazolidinones. The formation of thiol from thiourea, which is the key intermediate in thiazolidinone synthesis, invariably involves the $-NH-$ group adjacent to more electron withdrawing subunits.

Thiazolidinone derivatives possess types of biological activities[1-3] and also find industrial uses[4]. Only a few reports on the synthesis of these compounds from unsymmetrical thioureas and $\alpha$-halo acids or esters are available in the literature[5-8]. In most of these reports thioureas substituted with aromatic and heterocyclic moieties at either nitrogen have been employed. Although the formation of thiol compound, which is the key intermediate in these syntheses, has been claimed to involve the $-NH-$ group adjacent to heterocyclic moiety.

However, reverse mechanism is claimed by other investigators[5]. None of the authors have established the authenticity of the structures. This prompted us to synthesize thiazolidinones from thioureas (**1**) possessing different types of substituents and rationalise their mode of thiolisation from the degradation studies of the products. Following types of thioureas were used: (i) $N^1$-(4-aryl-2-thiazolyl-)-$N^2$-allyl-, $N^1$-phenyl-$N^2$-allyl-, $N^1$-(2-pyridyl)-$N^2$-allyl-, $N^1$-(2-pyridyl)-$N^2$-methyl-thioureas, (ii) $N^1$-phenyl-$N^2$-cycloalkyl-thioureas, (iii) $N^1$-cyclohexyl-$N^2$-allylthiourea and (iv) $N^1$-phenyl-$N^2$-(substituted phenyl)thioureas. These thioureas may give thiazolidinones of the type **2** or **3** when the thioureas of the type (i) were reacted with monochloroacetic acid in the presence of anhyd. sodium acetate in ethanol, crystalline solids were isolated. TLC of these compounds gave only one spot indicating the formation of a single compound in each case. The hydrolysis of these solids with ethanolic HCl gave an insoluble material which on characterisation was found to be 3-allylthiazole-2, 4-dione (**4**, $\phi'$ = allyl). The soluble fraction of the hydrolysate, after basification with ammonia furnished the respective amines. If the thiolisation would have occurred in




the reverse direction, we would have obtained 3-aryl/heteraryl thiazolidine-2, 4-dione (**5**, $\phi$ = aryl/heteraryl) and allyl amine. The IR spectra of the thiazolidinone **2** ($\phi$ = thiazolyl-2, $\phi'$ = allyl) showed bands at 2900 and 1735 $cm^{-1}$ due to $-CH_2-$ and $>C=O$ functions respectively whereas the dione **4** ($\phi'$ = allyl) showed bands at 1740 and 1755 $cm^{-1}$ for the two carbonyl groups in different environments besides the band at 2910 due to methylene function. The thiazolidinones obtaned from $N^1$-pyridyl-$N^2$-allyl and $N^1$-phenyl-$N^2$-allyl-thioureas furnished 2-aminopyridine and aniline respectively after hydrolysis. 3-Allyl thiazolidine-2, 4-dione was also isolated in both the cases. Hydrolysis of the thiazolidinone obtained from $N^1$-pyridyl-2-methylthiourea, furnished 3-methylthiazolidine-2, 4-dione and 2-aminopyridine. However, thiazolidinones prepared from the unsymmetrical thioureas of the type (ii), on hydrolysis gave aniline and 3-cycloalkylthiazolidine-2, 4-diones and those obtained from thiourea of the type (iii) furnished 3-cyclohexylthiazolidine-2, 4-dione and allylamine. These observations indicate that the thiolisation of unsymmetrical thioureas in ethanolic medium invariably involved the $-NH-$ group adjacent to more electron withdrawing moieties. In the case of thioureas of the type (i), thiazole, pyridine and phenyl moieties are more electron withdrawing than allyl or methyl. Similarly, in the case of thioureas of the type (ii) phenyl group is more electron withdrawing than the cycloalkyl, and in thioureas of the type (iii) allyl is more electron withdrawing than the cyclohexyl moiety.

Since thiolisation is an important step in the formation of thiazolidinones the above observations were confirmed by hydrolysing the thiazolidinones prepared from phenyl-aryl-thioureas of the type (iv) in which one of the phenyl rings possessed substituents. When nitro or chloro substituent was present at para-

Table 1 — Characterisation Data of Thioureas (**1**) and Thiazolidinones (**2**)

| No. | $\phi$ | Thiourea (**1**) | | | Thiazolidinone (**2**) | | |
|---|---|---|---|---|---|---|---|
| | | m.p. °C | Sulphur (%) | | m.p. °C | Sulphur (%) | |
| | | | Found | Calc. | | Found | Calc. |
| | | $\phi'$ = Alltyl | | | | | |
| b | 4-Ph.Th | 170 | 24.0 | 23.3 | 173 | 19.8 | 20.3 |
| c | 4-*p*-$ClC_6H_4$.Th | 152 | 19.9 | 20.7 | 142 | 17.4 | 18.3 |
| d | 4-*p*-$OCH_3C_6H_4$.Th | 186 | 21.3 | 21.0 | 193 | 18.0 | 18.6 |
| e | Ph | 95 | 15.4 | 16.2 | 118 | 13.2 | 13.8 |
| f | 2-Pyridyl | 96 | 16.0 | 16.6 | 78 | 12.8 | 13.4 |
| | | $\phi'$ = Cyclohexyl | | | | | |
| g | 2-Pyridyl | 142 | 18.6 | 19.1 | 121 | 14.9 | 15.5 |
| | | $\phi'$ = Cyclohexyl | | | | | |
| h | Ph | 147 | 13.4 | 13.6 | 88 | 10.5 | 11.2 |
| i | Allyl | 65 | 15.7 | 16.2 | 105 | 13.0 | 13.5 |
| | | $\phi'$ = Phenyl | | | | | |
| j | *p*-$ClC_6H_4$ | 135 | 11.9 | 12.2 | 144 | 10.1 | 10.5 |
| k | *p*-$NO_2C_6H_4$ | 125 | 12.0 | 11.7 | 122 | 9.9 | 10.2 |
| | | $\phi'$ = *p*-$OCH_3.C_6H_4$ | | | | | |
| l | Ph | 138 | 11.9 | 12.4 | 161 | 11.4 | 10.7 |

Th: 2-thiazolyl

position of the phenyl ring, the hydrolysis of the thiazolidinones furnish 3-phenylthiazolidine-2,4-dione and the *p*-nitro- or *p*-chloroaniline. When methoxy substituent was present at para-position of the phenyl ring of the thiourea, the hydrolysis products of the thiazolidinone were aniline and 3-(*p*-methoxyphenyl)2, 4-thiazolidione.

Melting points reported are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 293 spectrophotometer. The characterisation data of **1** and **2** are given in Table 1.

*$N^1$-(2-Thiazolyl)-$N^2$-allylthiourea* (**1a**: *$\phi$ = 2-thiazolyl, $\phi'$ = allyl*)

A solution of 2-aminothiazole (1 g) and allyl isothiocyanate (0.99 g) in rectified spirit (10 ml) was refluxed on a water-bath for 6 hr. The precipitate was filtered and crystallised from ethanol to give **1a**, m.p. 124° (Found: S, 31.8. $C_7H_9N_3S_2$ requires S, 32.2%).

*2-(2-Thiazolylimino)-3-allyl-4-thiazolidinone* (**2a**: *$\phi$ = 2-thiazolyl; $\phi'$ = allyl*)

A mixture of $N^1$-(2-thiazolyl)-$N^2$-allylthiourea (1.99 g) and monochloroacetic acid (0.95 g) in ethanol (50 ml) was refluxed for 6 hr on a water-bath, excess ethanol evaporated and the reaction mixture poured into cold water. The solid obtained was filtered, washed several times with hot water and crystallised from ethanol to give **2a**; m.p. 102° (Found: S, 26.0. $C_9H_9N_3OS_2$ requires S, 26.8%) IR: 2900 ($-CH_2-$), 1735 (C = O).

Other thioureas and thiazolidinones (Table 1) were prepared in a similar manner.

*Hydrolysis of the products*

A mixture of thiazolidinone (0.5 g) in rectified spirit (25 ml) and concentrated HCl (6 ml) was refluxed on a water-bath for 8 hr, excess of alcohol distilled off and the residue extracted with boiling water. The water insoluble component after recrystallisation from ethanol gave 3-allylthiazolidiene-2, 4-dione as a colourless solid, m.p. 195° (Found: S, 19.7. $C_6H_7O_2NS$ requires S, 20.4%); IR: 2910 ($-CH_2-$), 1755 and 1740 (C = O). The aqueous solution, after removal of oily mass, was extracted with ether, and ether removed to give 2-aminothiazole as a colourless solid, m.p. 90°.

Similarly, hydrolysis of the thiazolidinones **2b-f**, **2g**, **2h-i**, **2j-k** and **2l** gave 3-allylthiazolidine-2, 4-dione (m.p. 195°) (Found: S, 19.7. $C_6H_7O_2NS$ requires S, 20.4%), 3-methylthiazolidine-2, 4-dione (m.p. 75°) (Found: S, 24.0. $C_4H_5O_2NS$ requires S, 24.4%), 3-cyclohexylthiazolidine-2, 4-dione (m.p. 164°)

(Found: S, 15.7. $C_9H_{13}O_2NS$ requires S, 16.1%)), 3-phenylthiazolidine-2, 4-dione (m.p. 136°) (Found: S, 16.2. $C_9H_7O_2NS$ requires S, 16.6%) and 3-(*p*-methoxy phenylthiazolidine-2, 4-dione (m.p. 160°) (Found: S, 13.8. $C_{10}H_9O_3NS$ requires S, 14.4%) respectively along with the corresponding amines.

The authors are thankful to Prof. A Nayak of P G Department of Chemistry, Sambal pur University for helpful discussion and valuable suggestions.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 782-783

# A Two-step Synthesis of 1-Hydroxy-3-methoxy-10-methylacridone: An Acridone Alkaloid

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*Received* 28 *August* 1986; *accepted* 18 *November* 1986

A two-step synthesis of 1-hydroxy-3-methoxy-10-methylacridone **1**, an acridone alkaloid is reported. The synthesis involved the preparation of 1,3-dihydroxyacridone **2** followed by direct methylation to give **1**.

Acridone alkaloids have generated considerable interest in view of the reported[1] antitumor activity of acronycine, an acridone alkaloid isolated from the Rutaceous plants, *Achronychia baucrii* and *A. vepris*. Though a five-step synthesis of 1-hydroxy-3-methoxy-10-methylacridone (**1**) was reported[2] as early as 1951, the occurrence of **1** was reported much earlier from natural sources by four different groups of worker[3–7]. In this note, we report a two-step synthesis of **1** (Chart 1).

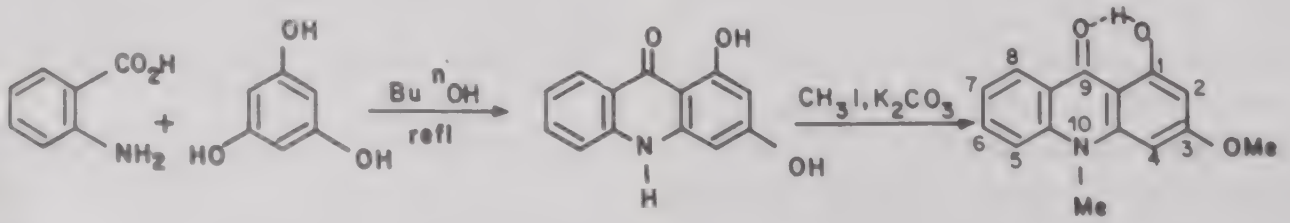
1,3-Dihydroxyacridone (**2**), prepared[8] by condensing anthranilic acid with phloroglucinol, on methylation afforded **1**, ($M^+$ 255), m.p. 163-65°. The UV spectrum of **1** was characteristic of 9-acridone[9]. Its IR spectrum exhibited bands at 1640 ($\nu C=O$) and 1155 (C-O-Me). The PMR spectrum of **1** was indicative of the presence of a strongly deshielded OH proton at $\delta$ 14.35 (*s*, 1H, $C_1-OH$) due to the peri carbonyl group at C-9 (ref. 9), and a deshielded aromatic proton at 8.26 (*d*, 1H, $C_9-H$) due to the neighbouring C-9 carbonyl group. The two aromatic protons at C-7 and C-6 appeared as a two-proton singlet at 7.8 while that at C-5 appeared as a one-proton multiplet at 7.30. The aromatic protons at C-4 and C-2 appeared as one-proton singlet each at 6.43 and 6.29 respectively[11,12]. The C-3 methoxy and N-methyl protons appeared respectively at 3.90 and 3.89 (*s* each, 3H each). The formation of **1** during the methylation of **2** indicated that $C_1-OH$ in 9-acridone can be methylated only under drastic condition.

1,3-*Dihydroxyacridone* (**2**)

A mixture of anthranilic acid (6.85 g), phloroglucinol (6.30 g), anhydrous zinc chloride (7 g) and *n*-butanol (150 ml) was refluxed for 8 hr with continuous removal of water. The reaction mixture was cooled, diluted with benzene-water (1:1, 100ml), the organic layer separated and dried ($K_2SO_4$). Removal of solvents under reduced pressure left an oily mass which was dissolved in hot and aqueous NaOH (5 %, 500 ml) and filtered. The filtrate on acidification with dil $H_2SO_4$ (5 %) afforded **2** (8 g), which was purified on a silica gel column to furnish a greenish-yellow product, m.p. 316-20° (d) [lit[8], m.p. 320° (d)].

1-*Hydroxy*-3-*methoxy*-10-*methylacridone* (**1**)

Compound (**2**, 100 mg) in dry acetone (50 ml) was refluxed with methyl iodide (5 ml) and anhydrous potassium carbonate (5 g) for 3 hr (TLC monitoring). The reaction mixture was filtered and the residue washed with dry acetone several times. The combined washings and the filtrate was concentrated under reduced pressure to a gummy mass, which was subjected to column chromatography over silica gel column. The petroleum ether-EtOAc (90:10) fractions afforded **1** as a bright yellow solid (60 mg), m.p. 174-76° (petroleum ether-EtOAc) (lit[2,4], m.p. 174-76°); UV (EtOH): 202, 229, 248, 262, 269, 294, 324 and 393 nm (log $\varepsilon$ 4.21, 4.24, 4.51, 4.67, 4.69, 4.12, 3.90 and 3.84); IR (nujol): 1640, 1600, 1560, 1515, 1380, 1280, 1240, 1220 and 1155; PMR (DMSO-$d_6$): $\delta$ 14.85 (*s*, 1H), 8.26 (*d*, 1H, $J$ = 7 Hz), 7.80 (*d*, 2H, $J$ = 3




2 1

CHART 1

Hz), 7.30 (*m*, 1H), 6.43 (*s*, 1H), 6.23 (*s*, 1H), 3.93 (*s*, 3H) and 3.83 (*s*, 3H); MS: *m/z* (rel:int): 255 ($M^+$, 100 %), 254 (22), 236 (56), 235 (18), 212 (12).

Financial assistance to one of the authors (M H B) by the Government of India under Indo-Bangladesh Cultural Exchange Programme is gratefully acknowledged.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 784-785

# Reaction of Acetylene with the Lignin Model Compound 1-(4-Hydroxy-3-methoxyphenyl)glycerol 2-Guaiacyl Ether under UV Irradiation

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*Received* 3 *February* 1986; *revised and accepted* 6 *November* 1986

Reaction of acetylene with the lignin model compound 1-(4-hydroxy-3-methoxyphenyl)glycerol 2-guaiacyl ether (**1**) under UV irradiation at different temperatures has been studied. Besides the degradation products, a compound has been isolated and assigned the structure **2** on the basis of IR and PMR spectral data.

An interesting use of lignin, a waste product from biomass, lies in its pyrolytic conversion into acetylene[1]. Since acetylene is available from biomass and mining (non-petroleum sources) and is highly reactive, we have investigated its reaction with a lignin model compound 1-(4-hydroxy-3-methoxyphenyl)glycerol 2-guaiacyl ether (**1**) under UV light.

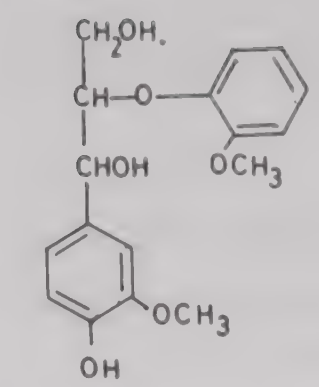
High temperature, high pressure reactions of acetylene with lignin sulphonates and guaiacol are known to produce partially soluble resins presumably from initially formed vinyl ethers[2]. Thermally initiated high pressure reactions for long periods (50 hr) invariably lead to resinous products without much chances to determine reaction variables that optimize preferred products.

Acetylene derivatives polymerize under UV irradiation catalyzed by metal carbonyls in halogen donating solvents or by Ziegler-Natta catalysis to give high molecular weight polymers[3]. It has been polymerised to oligomers with copper catalysts[4]. But uncatalysed photochemically initiated reaction of acetylene with phenolics at moderate temperature has not been described to our knowledge.

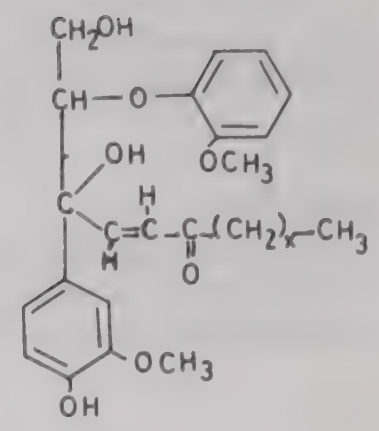
The reaction of acetylene with **1** under UV irradiation was carried out at 50°, 70° and 0°, and the results are given in Table 1.

Preparative TLC of the product mixture using $CHCl_3$-methanol (9:1) as irrigant gave four spots having $R_f$ 0.38, 0.48, 0.66 and 0.77, and the percent yields (taken with respect to the weight of the ether extract) were 52, 7.9, 8.8 and 3 respectively.

The reaction products at 0° differed from those at 50° and 70°. The oily product obtained from the reaction at 0° contained 33% of the unchanged compound **1** besides the products.




COMPOUND 1




COMPOUND 2

Table 1—Effect of Temperature on the Yield of the Reaction Products

| Temp. °C | White precipitate (mg) | Brown precipitate (mg) | I* (mg) | II† (mg) |
|---|---|---|---|---|
| 50 | 47 | 77 | 106 | 324 |
| 70 | 17 | 103 | 188 | 220 |
| 0 | none | 32 | 130 | 365 |
| 50‡ | 313 | 0 | 0 | 74 |
| 50** | 0 | 2 | 19 | 54 |

*Acetone soluble substance obtained from evaporation of the aqueous layer.
†Oil obtained from evaporation of the ether extract.
‡Control experiment (bubbling acetylene through a solution of 1.22 *N* KOH).
**Control experiment (irradiating 0.1 g of compound **1** in 1.22 *N* KOH solution without bubbling acetylene).

A conrol reaction without **1** at 50° gave a white precipitate essentially similar to that formed in the reactions at 50° and 70° with compound **1**. Solid state PMR and photoacoustic IR spectra were run on the product.

An additional control without acetylene was also run. A solution of compound **1** in aq. KOH as irradiated with UV light for 22 hr. In this case, the white precipitate was not formed, only the brown precipitate was obtained in 1.7% yield based on the starting compound **1** which was recovered in 55% yield from the preparative TLC of the oil obtained from the ether extract.

Of the various reaction products the white precipitate which formed a coating on the glass nearest to the light source was most interesting. The PAS-FT IR spectrum of this substance exhibited a carbonyl absorption at 1720 $cm^{-1}$; other bands which appeared at 2890, 2969, 1440, 1390 and 1170 $cm^{-1}$ did not give a clear evidence for unsaturation.

Analysis of the white precipitate, which showed C 75 and H 9.4%, definitely points to acetylene as the precursor since neither the model compound **1** nor acetone (a common impurity in acetylene) has such a high carbon content.

The compound isolated from the spot having $R_f$ 0.48 showed in its IR spectrum OH band at 3400, an α, β-unsaturated carbonyl peak at 1660 and peak at 960 $cm^{-1}$ corresponding to the *trans*-alkene C-H stretching. Its PMR spectrum in acetone-$d_6$ established the structure **2**. The PMR spectrum exhibited a doublet (1H) at δ 7.4 for an olefinic protons, a multiplet (7H) at 6.8-7.10 for the aromatic protons, a doublet (1H) at 6.57 corresponding to the other olefinic *trans*-hydrogen, a multiplet (12H) at 3.76-3.96 for the methoxy hydrogens and the protons at C-1 and C-2, and a doublet (3H) at 3.0 for the methyl protons.

The other products present in the ether extract were also isolated, identified and found to be degradation products which were not of interest to us.

Acetylene and KOH were used as such. A 450 W Imm mercury lamp (ACE Glass Inc., HK 273, USA) was used to irradiate the reaction mixture in the apparatus shown in Fig. 1.

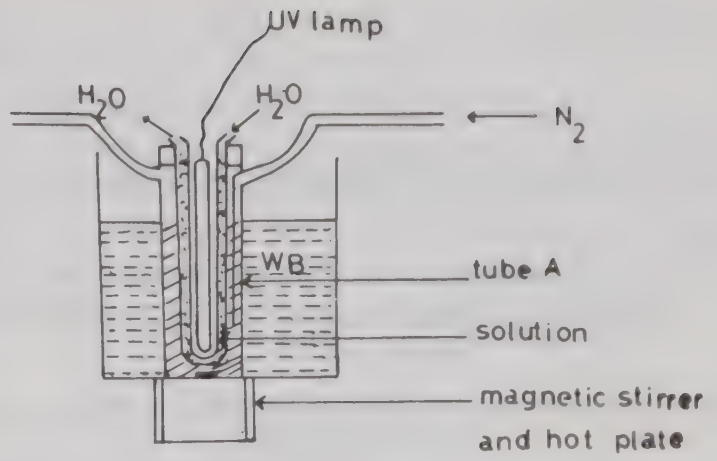



Fig. 1

*Synthesis of* 1-(4-*hydroxy*-3-*methoxyphenyl*)*glycerol*-2-*guaiacyl ether* (**1**)

It was prepared in five steps from vanillin[5]. Guaiacol was condensed with ethyl chloroacetate to yield ethyl 2-methoxyphenoxyacetate which in turn was condensed with benzylvanillin (obtained from benzylation of vanillin) using lithium diisopropylamide as the base to give an oily residue which was a mixture. A solution of 30 g of the mixture in 125 ml $CH_2Cl_2$ was chromatographed on a silica column using 0.1% methanol in $CH_2Cl_2$ as eluant with an elution rate of 250 ml/min, and 2.5% methanol in $CH_2Cl_2$ as a wash. Collection of the cuts right after the major peaks on each run gave the desired product after the evaporation of the solvent. A small sample was rechromatographed as above to give a single sharp peak. This compound was converted into carbamate and crystallised from ethanol. Only the erythroisomer would recrystallize in this step. The isomer was reduced by lithium aluminium hydride and then hydrogenated over Pd-C to give **1** in 40% yield.

*Reaction of* **1** *with acetylene under UV irradiation*

A solution of **1** (0.5 g) in 150 ml of 1.22 *N* KOH was put in the reaction vessel (Fig. 1) and nitrogen gas bubbled first through it for 5 min and then acetylene for 22 hr. The solution was irradiated with UV light for 22 hr. The experiment was carried out at 50°, 70° and 0°. At the end in the case of reactions at 50° and 70° a white precipitate appeared on the glass wall nearest to the light source. It was filtered off and washed many times with distilled water. The filtrate was acidified (and in the case of reaction at 0° the whole solution was acidified) when a brown precipitate was formed which was filtered off, and the filtrate extracted extracted with ether. The ether extract was dried (anhyd. $Na_2SO_4$) and solvent removed in a rotatory evaporator *in vacuo* at 40° to give an oil which was subjected to preparative TLC using 5% MeOH in diethyl ether as eluant. The remaining water soluble phase was evaporated and acetone soluble contents of the residue were removed.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 786-787

# Synthesis of Pyranoquinolines

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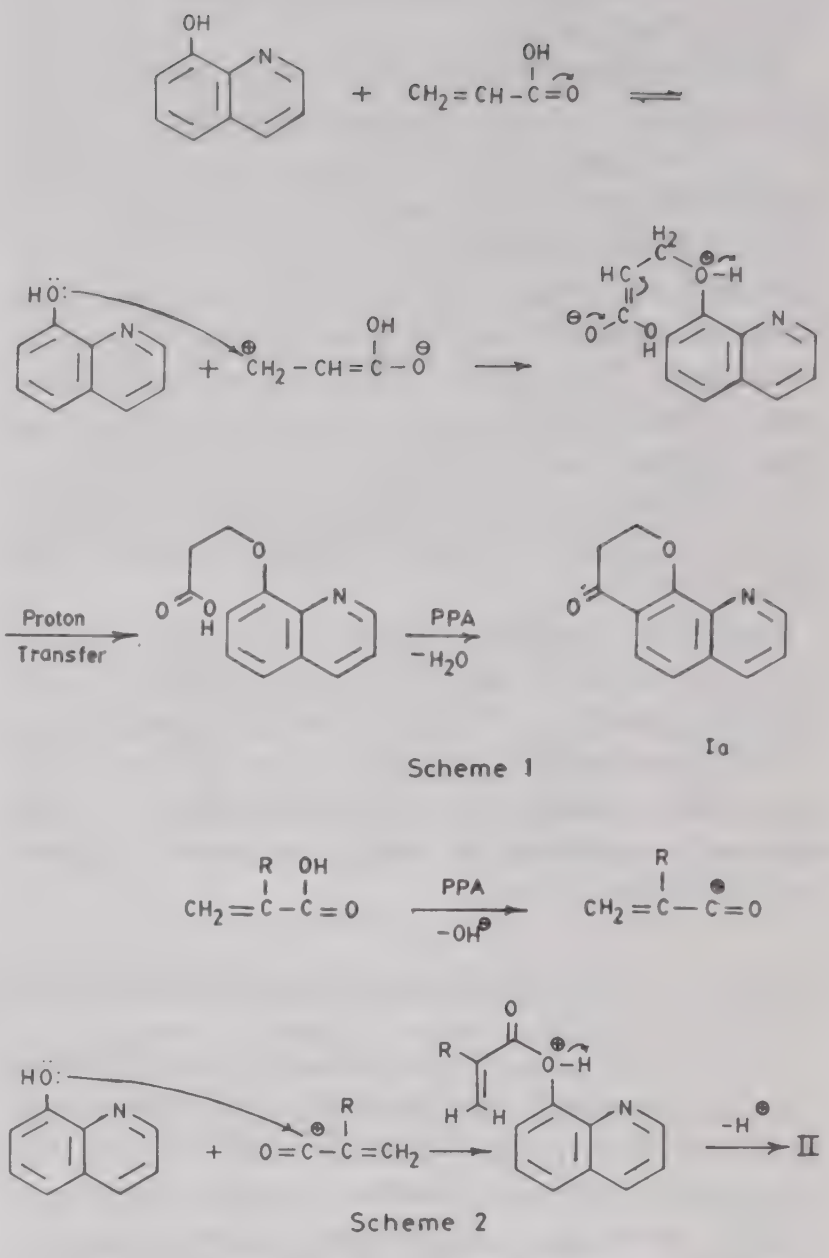
*Received* 19 *June* 1986; *revised and accepted*
18 *December* 1986

The reaction of hydroxyquinolines with $\alpha$, $\beta$-unsaturated acids in the presence of polyphosphoric acid affords in one-step the corresponding pyranoquinolines (I, III, IV).

Pyranoquinolines are the starting materials for the synthesis of quinolylhydantoins some of which are reported to possess antidiabetic acitivity[1]. The methods available hereto for the synthesis of the former are elaborate and inconvenient[2]. We describe here a simple one-step synthesis of pyranoquinolines.

8-Hydroxyquinoline (1 mol) was reacted with acrylic acid (1 mol) in the presence of PPA at 125° for 3 hr. Usual work-up of the reaction mixture afforded a dark solid which was chromatographed over neutral alumina using appropriate eluants (Table 1) to afford a crystalline solid which was found to be 3, 4-dihydro-2*H*-pyrano[3, 2-*h*]quinolin-4-one (Ia; Scheme 1). The structural assignments of Ia, which analysed for $C_{12}H_9NO_2$ ($M^+$ 199), were based on its spectral data. Its PMR ($CDCl_3$) spectrum displayed signals at $\delta$ 2.44 (2H, *t*, $-COCH_2$), 4.45 (2H, *t*, $OCH_2$), 7.44 (1H, *d*, $J$ = 9 Hz, $C_6$-H), 7.59 (1H, *t*, $C_8$-H), 8.00 (1H, *d*, $J$ = 9 Hz, $C_5$-H), 8.16 (1H, , *dd*, $J$ = 9 Hz and 2 Hz, $C_7$-H) and 9.06 (1H, , *dd*, $J$ = 3 and 2 Hz, $C_9$-H). Its IR (nujol) spectrum exhibited the carbonyl band at 1660 $cm^{-1}$.

Condensation of 8-hydroxyquinoline with crotonic acid in the presence of PPA (after column chromatography over neutral alumina) yielded 2-methyl-3, 4-dihydro-2*H*-pyrano[3, 2-*h*]quinolin-4-one (Ib).




The structure was established on the basis of its spectral data. The PMR ($CDCl_3$) spectrum of Ib showed signals at $\delta$ 1.72 (3H, *d*, $J$ = 6 Hz, $-CH_3$), 2.78 (2H, *d*, $J$ = 9 Hz, $-CH_2$), 4.87 (1H, *m*, $-CH$), 7.37 (1H, *d*, $J$ = 9 Hz, $C_6$-H), 7.50 (1H, *t*, $C_8$-H), 7.94 (1H, , *d*, $J$ = 9 Hz, $C_5$-H), 8.10 (1H, , *dd*, $J$ = 9 and 2 Hz, $C_7$-H) and 9.00 (1H, *dd*, $J$ = 9 Hz and 2 Hz, $C_9$-H). Its IR spectrum in potassium bromide showed the carbonyl absorption at 1660 $cm^{-1}$.

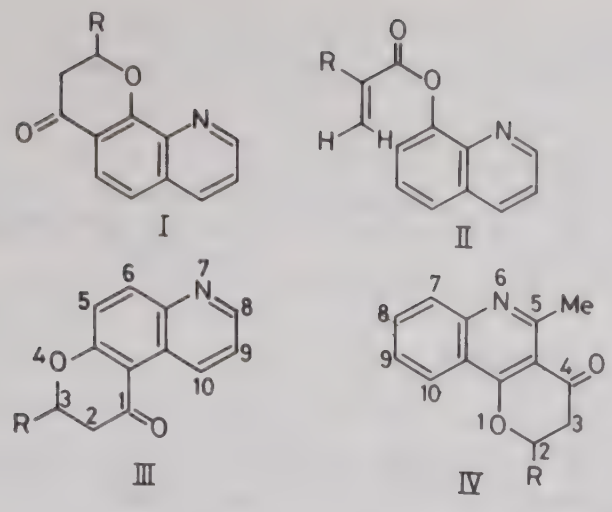
The reaction of 8-hydroxyquinoline with $\alpha$-methylacrylic acid yielded only an acrylate (II; Scheme 2) as gathered from its PMR ($CDCl_3$) spectrum which exhibited signals at $\delta$ 2.13 (3H, *s*, $-CH_3$), 5.78 (1H, , *t*, $J_{gem}$ = 0.3 Hz, $-CH$), 6.50 (1H, *t*, $-CH$), 7.25-7.80 (4H, *m*, $C_3$-, $C_5$-, $C_6$- and $C_7$-H), 8.13 (1H, *d*, $J$ = 9 Hz, $C_4$-H) and 8.84 (1H, *d*, $J$ = 3 Hz, $C_2$-H). Its IR spectrum in potassium bromide showed the carbonyl band at 1730 $cm^{-1}$.

It was found that 8-hydroxyquinoline underwent nuclear cyanoethylation with acrylonitrile giving the corresponding propionitrile derivative. However,

Table 1—Melting Points, Eluants used for the Separation of Various Products and Elemental Analyses

| Compd | R | Eluants* A : B | m.p. °C | Found (%) | | Calc. (%) | |
|---|---|---|---|---|---|---|---|
| | | | | C | H | C | H |
| Ia | H | 40 : 60 | 232-34 | 72.1 | 4.5 | 72.4 | 4.5 |
| Ib | Me | 60 : 40 | 135-37 | 72.9 | 5.2 | 73.2 | 5.2 |
| II | Me | 60 : 20 | 78-80 | 73.0 | 5.1 | 73.6 | 5.2 |
| III | Me | 70 : 30 | 115-17 | 73.1 | 5.3 | 73.2 | 5.2 |
| IV | Me | 50 : 50 | 106-8 | 73.0 | 5.7 | 74.0 | 5.7 |

*A = Light petroleum (60-80°); B = ethyl acetate.



I II III IV

the latter failed to undergo hydrolysis to the corresponding propionic acid which could undergo cyclisation to the required pyranoquinoline. The method reported here is thus superior and affords the desired pyranoquinolines in fairly good yields.

6-Hydroxyquinoline[3] failed to give the expected pyranoquinoline with acrylic acid and the starting material was recovered back. However, on condensation with crotonic acid 3-methyl-2, 3-dehydro-1*H*-pyrano[3, 2-*f*]-quinolin-1-one (III) was isolated. Its PMR spectrum ($CDCl_3$) showed signals at $\delta$ 1.55 (3H, *d*, $J = 9$ Hz, $-CH_3$), 2.77 (2H, *d*, $J = 9$ Hz, $-CH_2$), 4.57-4.89 (1H, *m*, $-CH$), 7.23 (1H, *t*, $C_6$-H), 7.25 (1H, *d*, $J = 9$ Hz, $C_9$-H), 8.02 (1H, *d*, $J = 9$ Hz, $C_{10}$-H), 8.79 (1H, *dd*, $J = 5$ and 2 Hz, $C_5$-H) and 9.69 (1H, *dd*, $J = 9$ and 2 Hz, $C_7$-H). Its IR spectrum in potassium bromide exhibited the carbonyl absorption at 1660 $cm^{-1}$.

The reaction of 4-hydroxy-2-methylquinoline[4] with crotonic acid yielded 2, 5-dimethyl-3, 4-dihydro-2*H*-pyrano[3, 2-*c*]quinolin-2-one (IV). Its PMR spectrum ($CDCl_3$) showed the signals at $\delta$ 1.65 (3H, *d*, $J = 6$ Hz, $-CH_3$), 2.81 (2H, *d*, $J = 9$ Hz, $-CH_2$), 2.94 (3H, *s*, $-CH_3$), 4.81 (1H, *m*, $-CH$) and 7.34-8.31 (4H, *m*, Ar-*H*). All other $\alpha$, $\beta$-unsaturated acids failed to give the pure products.

Melting points were taken in open capillary tubes and are uncorrected. The compounds were routinely checked by TLC, IR and PMR spectra. IR spectra were recorded on a Perkin-Elmer infrared 137 spectrophotometer and PMR spectra on a Varian spectrophotometer using TMS as internal standard.

*Reaction of hydroxyquinolines with $\alpha,\beta$-unsaturated acids: General procedure*

Hydroxyquinoline (1 mol) and an appropriate $\alpha$, $\beta$-unsaturated acid (1 mol) were heated in the presence of PPA [prepared from phosphorus pentoxide (10 g) and phosphoric acid (5 ml) preheated at 100° for 0.5 hr] at 120-125° for 3 hr with occasional shaking. The resulting mass obtained on decomposing the reaction mixture with ice cold water was kept overnight and extracted with chloroform. The extract was washed with aq. sodium hydrogen carbonate and subsequently with water. It was dried over anhyd. sodium sulphate. The solvent was removed by distillation to yield a reddish solid, which was separated by chromatography over neutral alumina to afford the required pyranoquinoline I, III or IV which crystallised from a suitable solvent (yield 25-30%).

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 788-789

# Reaction of 2-Mercaptobenzothiazole with Dichlorocarbene

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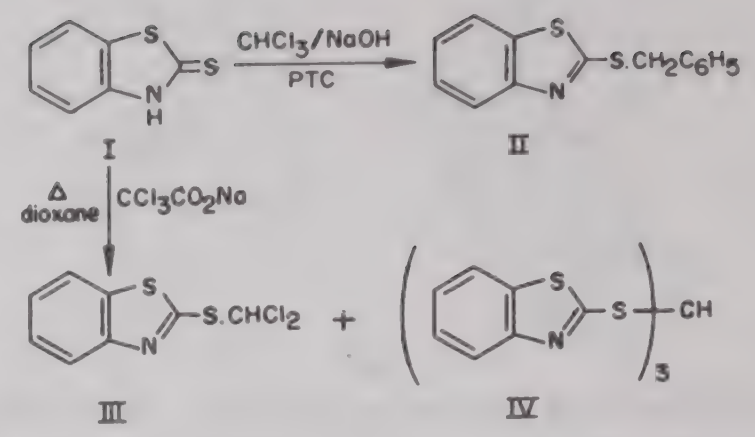
*Received* 8 *July* 1986; *revised and accepted* 22 *December* 1986

The reaction of dichlorocarbene with 2-mercaptobenzothiazole under Makosza conditions does not give any addition product, but results in an S-benzylated compound (II), whereas in anhydrous conditions it gives 2-(S-dichloromethylthio)benzothiazole (III) and tris(2-benzothiazolylthio)methane (IV).

Several heterocyclic compounds when reacted with dihalocarbenes are reported to undergo ring expansion and addition reactions[1,2]. Methodology using phase transfer catalyst in a two-phase system for generating halocarbenes has gained wide applications[3]. The heteroaromatic azoles and benzazoles offer a good potential to study their reaction with dihalocarbenes[4]. The results of the reaction of dichlorocarbene with 2-mercaptobenzothiazole (I) form the subject matter of this note.

Dichlorocarbene, generated under the phase transfer conditions, on reaction with 2-mercaptobenzothiazole (I) afforded a product (II) in 15% yield. The formation of II can be rationalized by the reaction of 2-mercaptobenzothiazole anion with phase transfer catalyst, triethylbenzylammonium chloride. The reaction when conducted in solvents such as dichloromethane and benzene also gave the product II indicating that dichlorocarbene is not involved in the formation of II, instead S-benzylation occurs by the quaternary salt. Such S-alkylations by the phase transfer catalysts are reported[5]. The product obtained was assigned the structure as 2-(S-benzylmercapto)benzothiazole (II) based on spectral data: Mass ($M^+$ at $m/z$ 257); PMR ($CDCl_3$) [δ 7.2-7.9 (*m*, 9H, aromatic H) and 4.5 (*s*, 2H, $-CH_2$)].

However, condensation of 2-mercaptobenzothiazole (I) with dichlorocarbene generated under neutral conditions from sodium trichloroacetate in dioxane afforded two compounds III and IV (15 and 40% yields respectively). The formation of III can be visualized via (2 + 2) cycloaddition of dichlorocarbene on C = S bond to give an episulphide intermediate, which further cleaves to give III. The structures of these compounds were corroborated by spectral data. High resolution mass spectrum of compound III revealed the ions at $m/z$ 248.9239 ($M^+$; $C_8H_5Cl_2NS_2$), 251 (M + 2), 253 (M + 4), 214 (M − 35) and 179 (M − 70). PMR ($CDCl_3$) spectrum of III showed peaks at δ 7.2-7.9 (*m*, 4H, aromatic H) and 6.10 (*s*, 1H, CH). Thus compound III could be assigned the structure as 2-dichloromethylthiobenzothiazole. The compound IV was assigned the structure as tris(2-benzothiazolylthio)methane (IV) on the basis of the following spectral data. The high resolution mass spectrum showed the $M^+$ at $m/z$ 510.9431 ($C_{22}H_{13}N_3S_6$) and the fragment ions at $m/z$ 344.9664 and 177.9779; PMR ($CDCl_3$): δ 7.2-7.67 (*m*, 12H, aromatic H), 7.96 (*s*, 1H, methine H); CMR ($CDCl_3$): δ 162.69, 152.89, 136.04, 126.40, 125.10, 122.66 and 121.30 (benzothiazolyl carbons), 57.16 (methine carbon). In the off-resonance proton decoupled spectrum, except for the signals at δ 162.69, 152.89 and 136.04 (tertiary carbons), all other signals are split into doublets.




Thus, the above results show that under PTC conditions, benzylation of the thiolate ions of I with TEBA occurs to give II, whereas in anhydrous conditions, reaction of dichlorocarbene with I leads to the insertion product III which can further react with I forming IV.

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 283B spectrophotometer, PMR and CMR spectra on a JEOL FX 90Q instrument using TMS as internal standard and mass spectra on Micro Mass 7070H instrument.

*Reaction of 2-mercaptobenzothiazole with dichlorocarbene generated under phase transfer conditions*

To 2-mercaptobenzothiazole (I; 1g) in chloroform (30 ml) were added triethylbenzylammonium chloride (0.016 g) and triethylenediamine (0.007 g) as phase transfer catalysts. To the above stirred solution aq. sodium hydroxide (35%, 1.5 ml) was added dropwise and the reaction mixture stirred at ambient temperature. The progress of the reaction was monitored by TLC. After 6 hr, the reaction mixture was

worked-up. The chloroform layer was separated and the crude material purified on a silica gel column using chloroform as eluant to give II in 15% yield (Found: C, 65.4; H, 4.3. $C_{14}H_{11}NS_2$ requires C, 65.4; H, 4.3%).

*Reaction of I with dichlorocarbene under neutral conditions*

A solution of sodium trichloroacetate (2.3 g) in dry dioxane (20 ml) was added to a solution of I (1 g) in dioxane (10 ml) and the reaction mixture stirred at 100° for 8 hr. After completion of the reaction, sodium salt formed by the decomposition of sodium trichloroacetate was filtered and the solvent distilled. The residue, thus obtained, was chromatographed over silica gel column using benzene as eluant to give III and IV as pure products in 15 and 40 per cent yields respectively (Found: C, 38.5; H, 2.0. $C_8H_5Cl_2NS_2$ requires C, 38.6; H, 2.0% for compound III, and Found: C, 51.7; H, 2.6. $C_{22}H_{13}N_3S_6$ requires C, 51.7; H, 2.6% for compound IV).

One of the authors (J S R) is thankful to the CSIR, New Delhi for the award of a junior research fellowship.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 790-793

# Pyrolysis-Chemical Ionization Mass Spectra of Plant Glycosides

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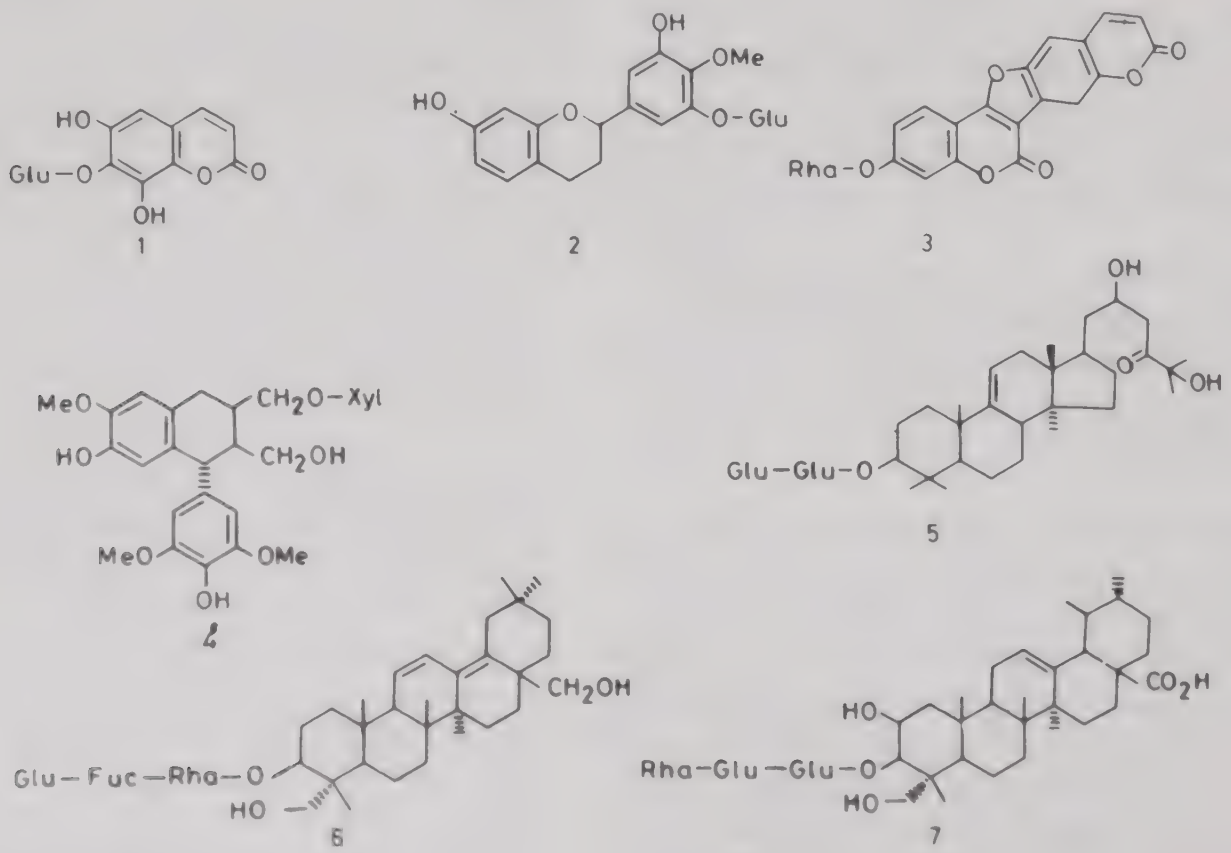
*Received* 10 *June* 1986; *revised and accepted* 28 *November* 1986

Pyrolysis-chemical ionization mass spectra of a few glycosides show that this technique allows a partial characterisation of the sugar moieties in the glycosides. Adduct ions and fragment ions formed by successive loss of water molecules are prominent under both positive ion CI($NH_3$) and negative ion CI($Cl^-$) conditions. Characteristic substitution ions corresponding to loss of water from the ammonium adduct ions are observed in the CI ($NH_3$) spectra.

Mass spectrometry of naturally occurring plant glycosides requires special techniques because of the low volatility of the underivatised molecules. Newer ionization techniques such as desorption chemical ionization (DCI)[1], field desorption (FD)[2], fast atom bombardment (FAB)[3] and FAB combined with collisional activation (CA)[4] have extensively been used for the mass spectral analysis of such compounds. However, such facilities are not always available. An alternative technique with some limitations is the pyrolysis-chemical ionization (Py-CI) mass spectrometry[5]. On heating, glycosides undergo degradation to give smaller molecules which may be ionized by a suitable technique such as CI[6,7] or FI[8]. We report herein the results of our studies on the Py-CI mass spectra of a few plant glycosides (**1-7**) under both positive and negative ion conditions.

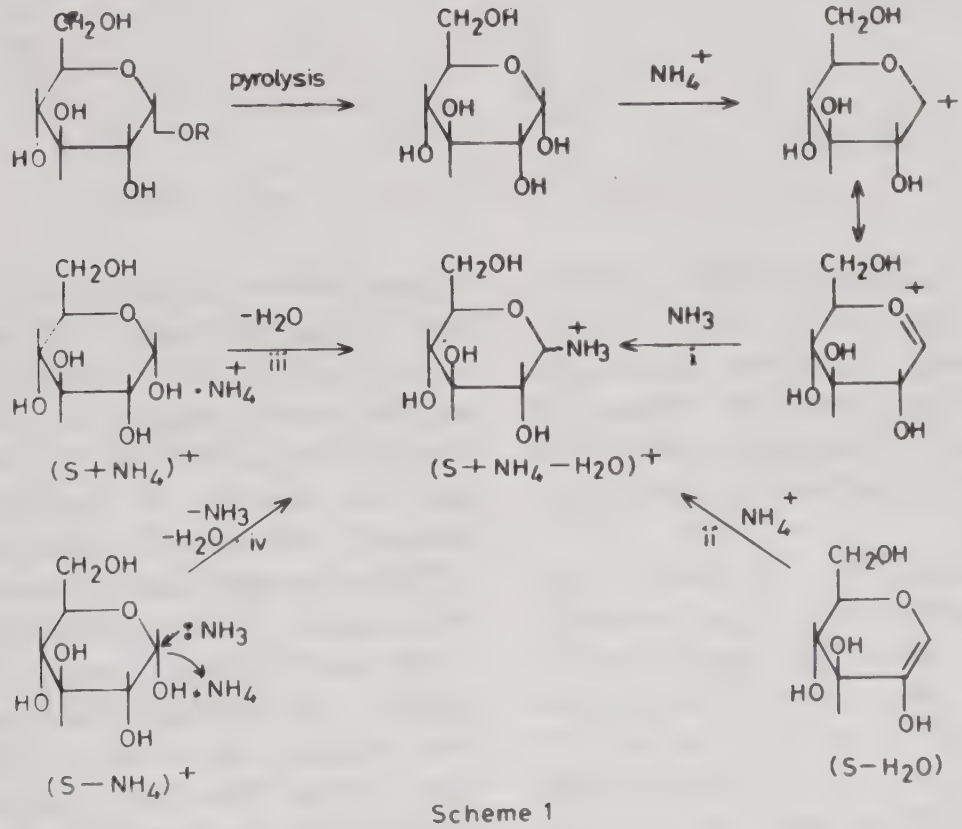
The major ions and their abundances in the Py-CI mass spectra of the glycosides **1-7** are given in Table 1. Cleavage at either side of the glycosidic oxygen leads to the formation of sugar and aglycon moieties which on ionization produce the adduct ions of sugar $(S+NH_4)^+$ and aglycon $(A+NH_4)^+$. Loss of $H_2O$ from $(S+NH_4)^+$ gives rise to an abundant ion, the *m/z* value of which corresponds to that of the molecular ion of the sugar. The observation of this ion in the CI ($NH_3$) spectra of sugars and glycosides has previously been reported by several workers[9-12] and this ion results from a substitution of one of the hydroxyl groups by amino group. The Py-CI spectrum of **4** recorded in the presence of $^{15}NH_3$ is shown in Fig. 1. The $(S+NH_4)^+$ and the ions corresponding to successive losses of $H_2O$ from $(S+NH_4)^+$ show a shift of one mass unit indicating the incorporation of $^{15}N$ thus confirming the substitution process. There can be four possible pathways for the formation of the substitution ion $(S+NH_4-H_2O)^+$ as shown in Scheme 1, viz. (i) by the action of neutral $NH_3$ on the oxonium ion formed by cleavage of the glycosidic bond[10], (ii) by the addition of $NH_4^+$ to thermally formed $(S-H_2O)$[13], (iii) by the direct loss of $H_2O$ from $(S+NH_4)^+$[14] and (iv) by the action of $NH_3$ on $(S+NH_4)^+$ in an $S_N2$ manner[15]. The




†CDRI Communication No. 3907

Table 1—Abundances (%, in parentheses) of Major Ions in the Py-CI ($NH_3$) Spectra of 1-7 (values in $m/z$)

| Ion | Glycoside | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| $(A+NH_4)^+$ | 212 | 306 | | 438 | 492 | 474 | 506 |
| | (100) | (80) | | (100) | (99) | (18) | (28) |
| $(A+H)^+$ | 195 | 289 | | 421 | 475 | 455 | — |
| | (11) | (100) | | (18) | (9) | (12) | |
| $(S+NH_4)^+$ | 198 | 198 | 182 | 168 | 198 | 182 | 198 |
| | (2) | (1) | (13) | (12) | (3) | (6) | (28) |
| | | | | | | | 182 |
| | | | | | | | (16) |
| $(S+NH_4-H_2O)^+$ | 180 | 180 | 164 | 150 | 180 | 180 | 180 |
| | (8) | (86) | (100) | (20) | (100) | (33) | (49) |
| | | | | | | 164 | 164 |
| | | | | | | (44) | (100) |
| $(S+NH_4-2H_2O)^+$ | 162 | 162 | 146 | 132 | 162 | 162 | 162 |
| | (5) | (39) | (52) | (15) | (26) | (8) | (12) |
| | | | | | | 146 | 146 |
| | | | | | | (100) | (16) |
| $(S.S+NH_4-H_2O)^+$ | | | | | 342 | 326 | 326 |
| | | | | | (10) | (50) | (21) |




Scheme 1

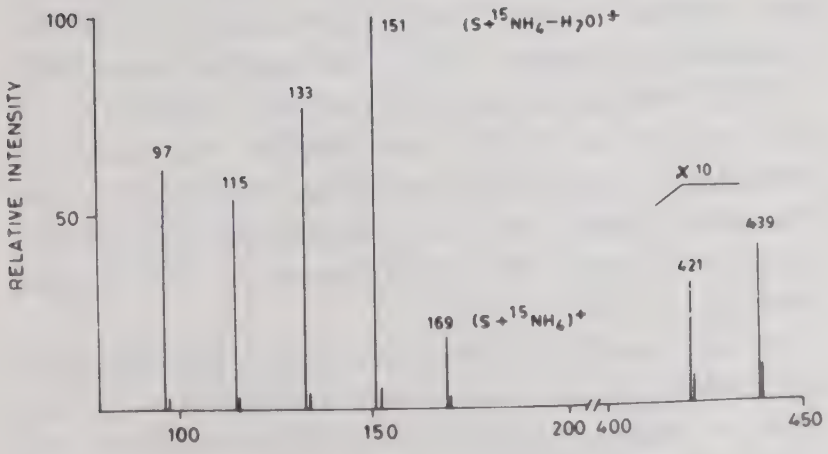



Fig. 1—Py−CI($^{15}NH_3$)spectrum of Pygcoside(4)

operation of process (iii) could not be confirmed as no metastable peak was observed for the loss of $H_2O$ from $(S+NH_4)^+$ ion. Further, the comparatively low abundance of $(S+NH_4)^+$ ion suggests no significant contribution from process (iv). Under Py-CI conditions it appears that the abundant $(S+NH_4-H_2O)^+$ and $(S+NH_4-2H_2O)^+$ ions are produced mainly by $NH_4^+$ attachment to the thermally formed neutral fragment $(S-H_2O)$ (process ii).

The appearance of these characteristic ions together with ions formed by further loss of $H_2O$ is indicative of the nature of the sugar units in a glycoside. For

Table 2—Abundances (%, in parentheses) of Major Ions in the Py-NCI($Cl^-$) Spectra of **1-7** (values in *m/z*)

| Ion | Glycoside | | | | | | |
|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
| $(A+Cl)^-$ | 229 (100) | 323 (100) | — | 455 (100) | 509 (10) | 491 (10) | 523 (7) |
| $(A-H)^-$ | 193 (92) | 287 (18) | — | 419 (16) | — | — | — |
| $(S+Cl)^-$ | 215 (4) | 215 (7) | 199 (29) | 185 (72) | 215 (9) | 215 (6) | 215 (95) |
| | | | | | | 199 (23) | 199 (48) |
| $(S+Cl-H_2O)^-$ | 197 (60) | 197 (74) | 181 (100) | 167 (90) | 197 (100) | 197 (39) | 197 (75) |
| | | | | | | 181 (19) | 181 (39) |
| $(S+Cl-2H_2O)^-$ | 179 (12) | 179 (28) | 163 (27) | 149 (45) | 179 (10) | 179 (13) | 179 (54) |
| | | | | | | 163 (100) | 163 (100) |
| $(S.S+Cl-H_2O)^-$ | | | | | 359 (23) | 343 (49) | 359 (42) |
| | | | | | 341 (1) | 327 (4) | 343 (30) |
| Others | | 121 (42) RDA | | | | 325 (6) | 341 (7) 325 (8) |

instance, the presence of ions at *m/z* 198 $(S+NH_4)^+$, 180 $(S+NH_4-H_2O)^+$ and 162 $(S+NH_4-2H_2O)^+$ indicates a sugar having molecular weight 180 (hexose), while a series of ions at *m/z* 182, 164 and 146 and at *m/z* 168, 150 and 132 indicate sugars having molecular weights 164 (deoxyhexose) and 150 (pentose) respectively.

Pyrolysis of glycosides also produces oligosaccharide units if present in the original molecule. This gives information about the arrangement of sugars in the glycoside. The presence of two glucose units in **5** is indicated by the ion at *m/z* 342 corresponding to $(S.S+NH_4-H_2O)^+$. The *m/z* value of this ion also indicates the terminal two sugars in a compound having more than two sugars. For example, in **6** and **7** this peak appears at *m/z* 326 showing thereby the presence of sugars having molecular weights 180 and 164 linked together.

Similar information is also obtainable from pyrolysis-negative chemical ionization ($CI^-$) spectra of the underivatised glycosides which show abundant chloride attachment ions. The major ions in the spectra of **1-7** along with their abundances are listed in Table 2 which clearly shows the parallel behaviour of these compounds under CI ($NH_3$) and NCI ($Cl^-$) conditions. $(A+Cl)^-$, $(S+Cl)^-$, $(S+Cl-H_2O)^-$, $(S+Cl-2H_2O)^-$ and $(S.S+Cl-H_2O)^-$ are the characteristic ions observed in the spectra suggesting thereby that these ions are formed by $NH_4^+$ and $Cl^-$ attachment to the respective neutral fragments formed thermally. It may be pointed out here that similar ions, formed by thermal cleavage followed by chloride ion attachment, were also observed in the direct exposure negative chemical ionization ($Cl^-$) spectrum of sucrose[13].

The compounds used in this study were available in this Institute. The glycosides **1-7** gave the expected $(M+H)^+$ and $(M+Na)^+$ ions in their field desorption spectra. The pyrolysis-chemical ionization spectra were recorded on a Jeol D-300 mass spectrometer fitted with a JMA 2000 data system. Pyrolysis was carried out by heating the sample to 300°C in a solid probe inside the ion source. The $^{15}NH_3$ CI spectra were recorded using $^{15}NH_4Cl$ (99 atom % N, MSD isotopes) to generate $^{15}NH_3$. The sample mixed with $^{15}NH_4Cl$ was heated in a solid probe to 250-300°C. A 1:10 mixture of $CHCl_3$ and MeOH was used to generate $Cl^-$ ions while recording NCl spectra. The ion source conditions were: electron energy, 200 eV, emission current, 300 $\mu$A; temperature, 200 C, and pressure, $1.5 \times 10^{-5}$ torr.

We are thankful to Dr R P Rastogi for providing the glycoside samples. Grateful acknowledgement is also made to RSIC, Lucknow where the mass spectral studies were carried out.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 794-796

# Fragmentation Pathways of the Molecular Ions of 1,3,4,5-Tetraarylimidazolidine-2-thiones under Positive & Negative Ionization Conditions†

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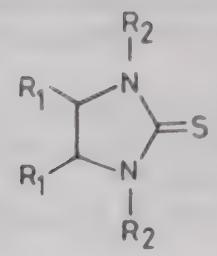
*Received* 26 *May* 1986; *revised and accepted* 31 *December* 1986

A comparative study of the fragmentation pathways of 1,3,4,5-tetraarylimidazolidine -2-thiones (**1-6**) under positive and negative ionization conditions has shown that the molecular ions are more stable under positive ionization conditions than under negative ionization conditions. Even though some of the fragment ions have the same *m/z* values in the positive and negative ion spectra, they have different elemental compositions under both the conditions. A 1,3-aryl migration from nitrogen to carbon leads to a characteristic skeletal rearrangement ion in the positive ion spectra.

The fragmentation pathways of heterocyclic compounds under positive ion electron impact (EI) have been well-established[1]. However, a very few studies have been carried out on their fragmentation modes under negative ionization conditions. As there is no report on the mass spectra of 1,3,4,5-tetraarylimidazolidin-2-thiones, we have undertaken a study on the fragmentation pathways of the molecular ions of such compounds (**1-6**) under both positive and negative ionization conditions and the results are presented here.

The synthesis of these compounds has been reported elsewhere[2]. Their mass spectra were recorded on a Jeol D-300 mass spectrometer attached to a JMA 2000 data system. The ion source conditions were: electron energy, 70 eV; emission current, 100 μA (positive) and 300 μA (negative); and temperature, 200°C. The samples were introduced through the direct inlet system and heated to 150-200°. The high resolution mass spectra (HRMS) were recorded at a resolution of 5000 using the data system under both positive and negative ionization conditions. The high voltage scan metastable peak measurements were made on a Jeol OISG 2 mass spectrometer at 70 eV under positive ionization conditions.



1 $R_1 = R_2 = Ph$

2 $R_1 = o\text{-}MeC_6H_4$, $R_2 = Ph$

3 $R_1 = m\text{-}MeC_6H_4$, $R_2 = Ph$

4 $R_1 = Ph$, $R_2 = p\text{-}MeC_6H_4$

5 $R_1 = m\text{-}MeC_6H_4$, $R_2 = p\text{-}MeC_6H_4$

6 $R_1 = o\text{-}MeC_6H_4$, $R_2 = p\text{-}MeC_6H_4$

## Positive ion spectra

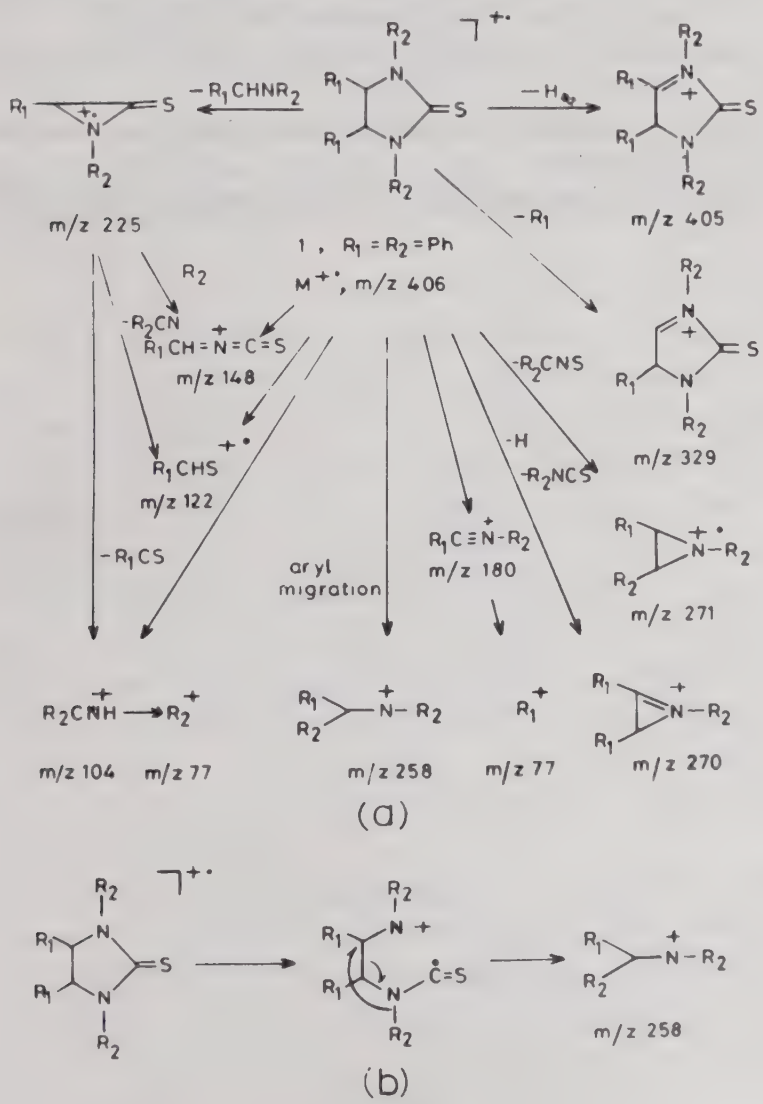
The presence of a five-membered heterocyclic ring having aryl groups leads to stable molecular ions[3] and consequently the base peaks in the positive ion electron impact spectra of **1-6** correspond to the respective $M^+$. The fragmentation pathways of the molecular ion of **1** are shown in Scheme 1 and the abundance of the major ions in the spectra of **1-6** and HRMS data of **1** are given in Table 1. The fragmentation pathways shown in Scheme 1 are supported by the appearance of the corresponding metastable peaks in by high voltage scan. Cleavage α to the C≡N bond leads to loss of H and $R_1$ while rupture of the ring α to the thiocarbonyl group gives rise to most of the other fragment ions as in the case of 1,5-disubstituted imidazolidinones[4]. The ion at *m/z* 180 in **1** can be either $(R_1CH=CHR_1)^+$ or $R_1C\equiv NR_2$. High resolution mass measurement of this ion shows that it has an elemental composition $C_{13}H_{10}N$. The presence of $R_2$ in this ion is also indicated by appropriate shifts in the substituted compounds.

The ion at *m/z* 258 in **1** can arise only via migration of one of the phenyl groups. High resolution mass measurements and shifts in the spectra of the substituted compounds indicate that this ion is composed of one $R_1$ and both the $R_2$ groups and has one nitrogen atom. A metastable peak appeared in high voltage scan for its formation directly from the $M^{+\cdot}$. A mechanism for this process involving an aryl migration to carbon is shown in

†CDRI Communication No. 3858

Table 1—Ion Abundances (%) in the Positive Ion EI Spectra of **1-6** and HRMS Data of **1**

| Ion | Compound | | | | | | HRMS data of **1** | |
|---|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** | *m/z* value (Obsd) | *m/z* value (Calc.) |
| $M^{+\cdot}$ | 406 (100) | 434 (100) | 434 (100) | 434 (100) | 462 (100) | 462 (100) | 406.1483 | 406.1502 |
| $(M-H)^+$ | 405 (70) | 433 (65) | 433 (66) | 433 (63) | 461 (68) | 461 (68) | 405.1424 | 405.1400 |
| $(M-R_1)^+$ | 329 (1) | 343 (12) | 343 (1) | 357 (1) | 371 (1) | 371 (18) | — | — |
| $(M-R_2NCS)^{+\cdot}$ | 271 (7) | 299 (8) | 299 (7) | 285 (7) | 313 (6) | 313 (12) | 271.1388 | 271.1360 |
| $(M-R_2NHCS)^+$ | 270 (7) | 298 (3) | 298 (4) | 284 (6) | 312 (5) | 312 (4) | 270.1259 | 270.1281 |
| $(M-R_1NC_2HS)^+$ | 258 (8) | 272 (7) | 272 (5) | 286 (11) | 300 (11) | 300 (6) | 258.1245 | 258.1281 |
| $(M-R_1CHNR_2)^{+\cdot}$ | 225 (53) | 239 (37) | 239 (22) | 239 (38) | 253 (47) | 253 (40) | 225.0656 | 225.0611 |
| $R_1C{\equiv}\overset{+}{N}R_2$ | 180 (25) | 194 (28) | 194 (18) | 194 (17) | 208 (20) | 208 (27) | 180.0810 | 180.0812 |
| $R_1CH=\overset{+}{N}=C=S$ | 148 (9) | 162 (7) | 162 (6) | 148 (7) | 162 (7) | 162 (4) | 148.0203 | 148.0220 |
| $R_1CHS^+$ | 122 (28) | 136 (13) | 136 (10) | 136 (25) | 136 (35) | 136 (35) | 122.0198 | 122.0190 |
| $R_2CNH^+$ | 104 (17) | 118 (7) | 118 (3) | 118 (18) | 118 (22) | 118 (18) | 104.0494 | 104.0500 |

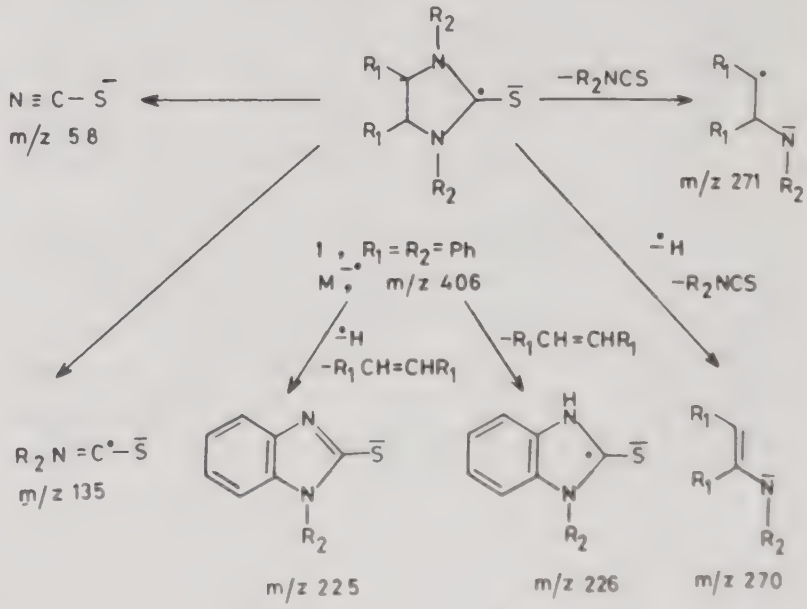



Scheme 1

Scheme 1b. Even though there are several reports on 1,3-aryl migration, no such rearrangement ions were observed in the mass spectra of 1,5-disubstituted compounds studied earlier[4].

**Negative ion spectra**

The molecular anions of the thiones **1-6** are not stable enough to give abundant $M^-$ peaks in their electron impact negative ion spectra. The major ions and their relative abundances in the negative ion spectra of **1-6** and the HRMS data of **1** are




Scheme 2

Table 2—Ion Abundances (%) in the Negative Ion EI Spectra of **1-6** and HRMS Data of **1**

| Ion | Compound | | | | | | HRMS data of **1** | |
|---|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** | *m/z* value (Obsd) | *m/z* value (Calc.) |
| $M^-$ | 406 (8) | 434 (2) | 434 (19) | 434 (17) | 462 (7) | 462 (5) | — | — |
| $(M-R_2NCS)^-$ | 271 (18) | 299 (2) | 299 (23) | 285 (22) | 313 (6) | 313 (1) | 271.1318 | 271.1360 |
| $(M-R_2NHCS)^-$ | 270 (11) | 298 (4) | 298 (2) | 284 (2) | 312 (8) | 312 (2) | 270.1295 | 270.1281 |
| $(M-R_1C_2H_2R_1)^-$ | 226 (67) | 226 (100) | 226 (59) | 254 (36) | 254 (54) | 254 (100) | 226.0489 | 226.0564 |
| $(M-R_1C_2H_3R_1)^-$ | 225 (77) | 225 (57) | 225 (35) | 253 (18) | 253 (59) | 253 (36) | 225.0387 | 225.0485 |
| $R_2N=C-S^-$ | 135 (23) | 135 (44) | 135 (100) | 149 (20) | 149 (17) | 149 (20) | 135.0137 | 135.0142 |
| $N\equiv C-S^-$ *m/z* 58 | (50) | (20) | (14) | (20) | (100) | (18) | 57.9765 | 57.9750 |

given in Table 2. Even though some of the ions in the positive and negative ion spectra have the same *m/z* values, they probably have different structures as shown in Scheme 2. For instance, the ion at *m/z* 225 in the negative ion spectrum of **1** corresponds to the loss of stilbene and H from the molecular anion, while in the positive ion spectrum it is due to loss of $PhCH=NPh$ from $M^{+\cdot}$. This is also supported by different elemental compositions ($C_{14}H_{11}NS$ and $C_{13}H_9N_2S$) of the ion in the positive and negative ion spectra. The ion at *m/z* 58 present in the spectra of all the compounds (**1-6**) corresponds to $N\equiv C-S^-$ as confirmed by the abundance of the isotope peaks at *m/z* 59 and 60. Unlike the positive ion spectra, no ion corresponding to aryl migration is observed in the negative ion spectra.

Grateful acknowledgement is made to RSIC, Lucknow where the mass spectra were recorded.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 797-798

# Synthesis of a Typical Chalkone & a Flavanone of *Wyethia glabra*

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*Received* 13 *June* 1986; *revised and accepted* 29 *November* 1986

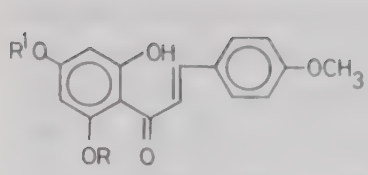
The constitution of a new chalkone as 2′, 4′, 6′-trihydroxy-4-methoxychalkone (**1**), isolated from *Wyethia glabra* has now been confirmed by its synthesis using 2′-hydroxy-4′, 6′-dibenzoyloxy-4-methoxychalkone (**1a**) as an essential intermediate. The structure of another compound as 5, 3′, 4′-trihydroxy-7-methoxyflavanone (**2**) (eriodictyol-7-methyl ether) isolated from the same source, has also been confirmed by its synthesis using vanillin as the starting material.

Two new compounds, 2′, 4′, 6′-trihydroxy-4-methoxychalkone (**1**) and eriodictyol-7-methyl ether (**2**) were isolated from *W yethia glabra* by Mc Cormick *et al.*[1]. Their structures were deduced by spectral data and degradation studies only. These two new natural products (**1** and **2**) have now been synthesised by convenient methods.

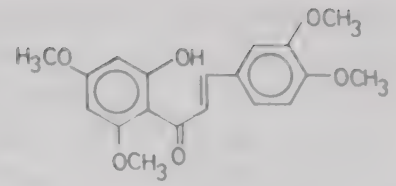
4, 6-Dibenzoyloxy-2-hydroxyacetophenone on condensation with anisaldehyde in ethanol in the presence of aq. KOH yielded 4′, 6′-dibenzoyloxy-2′-hydroxy-4-methoxychalkone (**1a**) which on debenzoylation with methanolic NaOH gave the desired natural product (**1**).

The synthesis of **2** is based on selective methylation study using aq. borax in alkaline medium. The selective methylation of any hydroxyl group in the case of flavanoids always occurs only in the presence of odd number of oxygen atoms present in the flavonoid nucleus including carbonyl oxygen of the flavanoid[2,3]. As in the case of tetrahydroxyflavanone only that hydroxyl group will be methylated which is not participating in the complex formation with aq. borax. The flavanone **2** contains 5, 7-dihydroxy system as well as 3′, 4′-dihydroxy system in which $C_7$-hydroxyl is preferentially methylated by means of selective protection of $C_5$-, $C_{3'}$- and $C_{4'}$-hydroxyl by aq. horax to give a complex (**6**).

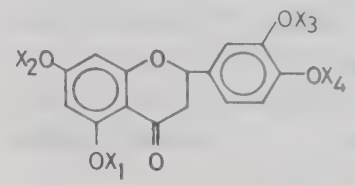
Eriodictyol-7-methyl ether (**2**) was synthesised using 5, 7, 3′, 4′-tetrahydroxyflavanone (**5**) as an essential intermediate which was obtained by the condensation of 2-hydroxy-4, 6-dimethoxyacetophenone[4] with 3, 4-dimethoxybenzaldehyde in alkaline ethanol followed by cyclization of the resulting 2′-hydroxy-4′, 6′, 3, 4-tetramethoxychalkone (**3**) with ethanolic $H_2SO_4$ and complete demethylation of 5, 7, 3′, 4′-tetramethoxy-



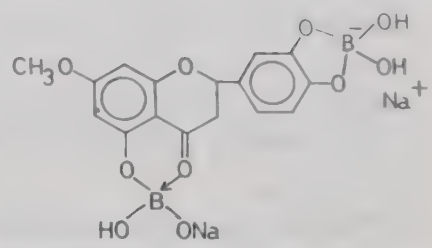
(1) $R_1, R' = H$
(1a) $R_1, R' = COC_6H_5$



(3)



(2) $X_1, X_3, X_4 = H$; $X_2 = CH_3$
(4) $X_1, X_2, X_3, X_4 = CH_3$
(5) $X_1, X_2, X_3, X_4 = H$



(6)

flavanone (**4**) using anhyd. $AlCl_3$ in dry benzene. Selective methylation of **5** using aq. borax in an alkaline medium afforded the required flavanone **2**.

The synthesised compounds **1** and **2** could not be directly compared with the natural products due to their non-availability. However, spectral data for the natural products were found to be in complete agreement with those of the synthesised compounds.

*4′, 6′-dibenzoyloxy-2′-hydroxy-3-methoxychalkone* (**1a**)

A mixture of 4, 6-dibenzoyloxy-2′-hydroxyacetophenone (1 g) and anisaldehyde (1.2 g) in ethanolic KOH was stirred for 2-3 hr, left at room temperature for 12 hr and worked-up as usual to give **1a** which crystallised from ethanol as yellow needles (1.5 g), m.p. 78-80°; PMR ($CDCl_3$): $\delta$3.90 (3H, *s*, $-OCH_3$), 5.92 (2H, *s*, $C_{3'}-$ and $C_{5'}$-H), 6.92 (2H, *d*, $J = 9$ Hz, $C_3-$ and $C_5-H$), 7.60 (2H, *d*, $J = 9$ Hz, $C_2-$ and $C_6-H$), 7.72 (11H, *d*, $J = 15$ Hz, $2 \times OCOC_6H_5$ and $C_\alpha-H$), 7.80 (1H, *d*, $J = 15$ Hz, $C_\beta-H$).

*2′,4′,6′-Trihydroxy-3-methoxychalkone* (**1**)

A solution of **1a** (1.0 g) in ethanol (50 ml) containing aq. NaOH (7 ml, 10%) was refluxed for 5 hr. After usual work-up it afforded **1** which crystallised from benezene-pet. ether, yield (0.5 g), m.p. 90-92 ; PMR ($CDCl_3$): $\delta$3.86 (3H, *s*, $-OCH_3$), 5.95 (2H, *s*, $C_{3'}$- and $C_{5'}$-H), 6.96 (2H, *d*, $J = 9$ Hz, $C_3-$ and $C_5-H$), 7.62 (2H, *d*, $J = 9$ Hz, $C_2-$ and $C_6-H$), 7.75 (1H, *d*, $J = 15$ Hz, $C_\alpha-H$), 8.95 (1H, *d*, $J = 15$ Hz, $C_\beta-H$); UV (MeOH): 360, 296 sh, + NaOMe: 392, 320, $+AlCl_3$ : 394, 309, $+AlCl_3-HCl$:382, 307 nm.

*2'-Hydroxy-4', 6', 3, 4-tetramethoxychalione* (**3**) *and its cyclisation to 5, 7, 3', 4'-tetramethoxyflavanone* (**4**)

A mixture of 2-hydroxy-4, 6-dimethoxyacetophenone[4] (1.5 g) and 3, 4-dimethoxybenzaldehyde (2.0 g) in ethanol in the presence of alkali was stirred and worked-up as usual to afford **3**, yield 2.0 g, m.p. 135-37°; PMR ($CDCl_3$): $\delta$3.90 (12H, *s*, 4 × $-OCH_3$), 5.92 (1H, *s*, $C_3$-H), 6.21 (1H, *s*, $C_{5'}$-H), 6.98 (1H, *d*, $J = 9$ Hz, $C_5-H$), 7.28 (2H, *s*, $C_2-$ and $C_6-H$), 7.72 (2H, *s*, $C_\alpha-$ and $C_\beta-H$).

Compound 3 on cyclization using ethanolic sulphuric acid gave **4**, yield 2.5 g, m.p. 117-20°; PMR ($CDCl_3$): $\delta$2.08 (1H, *dd*, $J = 4$, 16 Hz, $C_3-H_{eq}$), 3.00 (1H, *dd*, $J =$ 12, 16 Hz, $C_3-H_{ax}$), 3.89 (12H, *s*, 4 × $-OCH_3$), 5.29 (1H, *dd*, $J = 4$, 12 Hz, $C_2-H$), 7.41 (2H, *s*, $C_6-$ and $C_8-H$), 8.0 (3H, m, $C_{2'}-$, $C_{5'}$- and $C_{6'}$-H).

*Formation of eriodictyol* (**5**)

The tetramethoxyflavanone **4** (1 g) on complete demethylation using dry benzene and anhyd. aluminium chloride followed by usual work-up afforded 5, 7, 3', 4'-tetrahydroxyflavanone (**3**), yield 2 g; gave green colouration with ethanolic ferric chloride; PMR ($CDCl_3$): $\delta$2.10 (1H, *dd*, $J = 4$, 16 Hz, $C_3-H_{eq}$), 3.20 (1H, *dd*, $J =$ 12, 16 Hz, $C_3-H_{ax}$), 5.25 (1H, *dd*, $J = 4$, 12 Hz, $C_2-H$), 7.12 (2H, *s*, $C_6-$ and $C_8-H$), 7.50-7.79 (3H, *m*, $C_{2'}$- $C_{5'}$- and $C_{6'}$-H).

*Selective methylation of* **5**: *Formation of eriodictyol-7-methyl ether* (**2**)

Eriodictyol (**5**; 1.9 g) was treated with hot aq. borax solution (100 ml; 5%) and stirred. After the appearance of a green fluorescence, alkali (10 ml, 5%) was added to it during 4 hr, and the solution left at room temperature for 4 hr, acidified with cold dil. HCl and the precipitated **2** filtered and crystallised from ethanol, yield 0.3 g. It gave the Bergillini test[5] (a brownish green colouration with alcoholic ferric chloride) and dissolved in aq. $Na_2CO_3$ (10%); PMR($CDCl_3$): $\delta$ 2.81 (1H, *dd*, $J = 4$, 16 Hz, $C_3-H_{eq}$), 3.0 (1H, *dd*, $J =$ 12, 16 Hz, $C_3-H_{ax}$), 3.80 (3H, *s*, $-OCH_3$), 5.42 (1H, *dd*, $J = 4$, 12 Hz, $C_2$-H), 5.78 (1H, *s*, $C_5-OH$), 6.01 (1H, *s*, $C_6-H$), 7.08 (3H, *m*, $C_{2'}$-, $C_{5'}$- and $C_{6'}$-H); UV (MeOH): 329 (sh), 286, + NaOMe: 285, 350 (sh), + $AlCl_3$: 309, + $AlCl_3$: 309, 370 nm (sh).

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Indian Journal of Chemistry
Vol. 26B, August 1987, p. 799

# A New Isoflavone from Leaves of *Afrormosia laxiflora* Harms.

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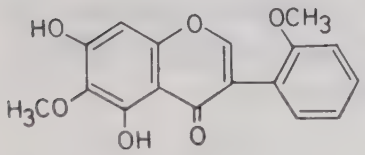
*Received* 13 *October* 1986; *accepted* 18 *December* 1986

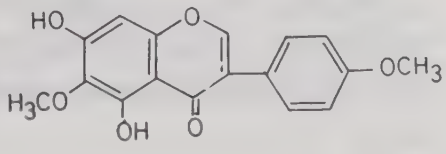
A new isoflavone, characterised (IR, UV, PMR and mass) as 5,7-dihydroxy-2′,6-dimethoxyisoflavone (I) and irisolidone, another known isoflavone have been isolated from the acetone extract of the leaves of *Afrormosia laxiflora* Harms.

In a broad programme on the flavanoid constituents of plant species[1-3], we undertook the chemical examination of *Afrormosia laxiflora* Harms. The results are reported in this note.

The acetone extract of the defatted leaves of *A. laxiflora* on chromatography over silica gel column afforded two yellow compounds as the major components. These were separated and purified by repeated column chromatography (silica gel) followed by preparative TLC over silica gel plates (benzene-pyridine-formic acid, 36:9:5). Compounds I and II recrystallised from MeOH as pale yellow and light yellow needles, m.ps 194° (I) and 192° (II) respectively. These two compounds gave characteristic colour reactions for isoflavones and UV spectra confirmed these to be isoflavones.



(I)



(II)

Compound I analysed for $C_{17}H_{14}O_6$ ($M^+$ *m/z* 314), formed a diacetate ($Ac_2O$/Py; m.p. 176-78°, white needles from $CHCl_3$-*n*-hexane) and a dimethyl ether ($Me_2SO_4$-acetone-$K_2CO_3$ method, m.p. 170° (Found: C, 64.72; H, 4.51. $C_{19}H_{18}O_6$ requires C, 64.96; H, 4.45%) indicating the presence of two OH groups. The 300 MHz PMR spectrum of I in $CDCl_3$ + DMSO-$d_6$ displayed doublets of 3H each at δ 3.74 and 3.81, assignable to $OCH_3$ protons, a one-proton signal at 7.96 ($C_2$-H) and chelated OH proton at 3.85, the presence of which was also confirmed by a bathochromic shift of the $\lambda_{max}$ in the presence of anhydrous $AlCl_3$ (ref. 4) and a broad band at 3400 $cm^{-1}$ in its IR spectrum. Bathochromic shift of 8 nm on the addition of sodium acetate[5] indicated the presence of a second hydroxyl group which was discernible in its PMR spectrum by a signal at δ 10.26 for H-7. A singlet at δ 6.57 (1H) could be assigned to an aromatic proton shielded by two *ortho* and one *para* oxygens. This singlet could possibly due to the C-6 proton of 5,7,8-trioxygenated isoflavone or the C-8 proton of 5,6,7-trioxygenated compound. The mass spectrum showed $M^+$ at *m/z* 314 (100%) and a peak at 299 (50%) corresponding to the loss of methyl from $M^+$ ion peak. This justified the placement of the methoxyl at C-6. In 8-methoxyl-5-hydroxyflavanoids the order is reversed and the predominant peak is the one resulting by the loss of methyl from $M^+$. The ring-B aromatic protons (4H) appeared as a multiplet (no $A_2B_2$ pattern), suggesting that the remaining methoxyl group could not be located at C-4′. The only position to be considered was C-2′ or C-3′. The absence of two *meta* coupled proton doublets in the PMR spectrum ruled out the possibility of the second methoxyl group at C-3′. A series of decoupling experiments showed that proton at δ 7.25 (1H, *dd*, $J$ = 8.0 and 2.3 Hz, H-6′) was coupled to the protons which appeared at 7.05 (H-5′) and 7.43 (H-4′). The proton appearing at δ 7.13 (H-3′) was coupled to the protons appearing at 7.43 ($J$ = 8.0 Hz) and 7.05 ($J$ = 2.3 Hz). The decoupling experiments strongly suggested the presence of the methoxy group at C-2′. On the basis of these data, compound (I) could be formulated as 5,7-dihydroxy-2′,6′-dimethoxyisoflavone.

Isoflavone (II), m.p. 192° was characterised as irisolidone[6] by direct comparison with an authentic sample.

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Indian Journal of Chemistry
Vol. 26B, August 1987, p. 800

# Stigmasta-7,16,25(26)-triene-3-O-$\beta$-D-glucopyranosyl-(1 → 5)-O-$\beta$-D-xylofuranoside: A New Saponin from the Fruits of *Cucumis momordica* (Duthie)

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*Received* 14 *February* 1986; *revised and accepted* 4 *December* 1986

A new saponin has been isolated from the fruits of *Cucumis momordica* (Duthie) and characterised as stigmasta-7-16-25(26)-triene-3-O-$\beta$-D-glucopyranosyl-(1→5)-O-$\beta$-D-xylofuranoside.

*Cucumis momordica* (N.O. Cucurbitaceae)[1,2] is commonly known as 'Phut' in Hindi and is reported to be useful in eye infections, ulcers, bronchitis, kidney troubles, burning of throat and chronic fever[3]. The seeds of this plant contain some fatty acids[4]. Cucumin[5] and Leptodermin[6] have already been reported to be present in its fruits.

In this investigation the methanol soluble part of the rectified spirit extract of its fruits when worked-up yielded a homogeneous saponin (TLC), molecular formula $C_{40}H_{64}O_{10}$ ($M^+$ 704), m.p. 158-59°, $[\alpha]_D^{22}$ +22.5 ($CHCl_3$); IR(KBr): 3420, 3055, 2900, 2810, 1650, 1630, 1430, 1408,1380, 1340, 1247, 1180, 1042, 1030, 978-950, 850-800; PMR($CDCl_3$) of acetyl derivative: $\delta$ 0.70 (*d*, 3H, sec. $CH_3$), 0.76 (*s*, 6H, 2 × $CH_3$, sec.), 0.81 (*m*, 3H, primary $CH_3$), 0.94 (*s*, 3H, tert. $CH_3$), 1.24-2.00 (complex *m*, 27, methylene protons), 5.50 (*dd*, 1H, vinylic H), 4.28 (*d*, 1H, $J$=7.2 Hz, anomeric 1′-H), 4.38 (*d*, 1H, $J$=7.0 Hz, anomeric 1″-H), 3.4-4.25 (*m*, 11H, sugar protons), 2.02 (*s*, 3H, OAc at C-2′), 2.09 (*s*, 3H, OAc at C-3′), 2.06 (*s*, 6H, OAc at C-2″ and C-3″), 2.04 (*s*, 3H, OAc at C-4″), 2.07 (*s*, 3H, OAc at C-6″); MS: *m/z* 704 ($M^+$), 541, 525, 410, 395, 392, 381, 314, 300, 271, 234, 216, 202.

On hydrolysis it afforded a genin and sugars identified as D-xylose and D-glucose (co-PC and co-TLC). The genin crystallized from pyridine as light yellow crystals, m.p. 167-68°, $[\alpha]_D^{22}$ 8.2 ($CHCl_3$), $C_{29}H_{46}O$, $M^+$ 410. It gave colour reactions characteristic of steroids[7,8]; IR(KBr): 3420, 3012, 3035, 3030, 2900, 2800, 1625, 1655, 1640, 1440, 1400, 1375, 1340, 1305, 1250, 1247, 1195, 1155, 1110, 1070, 1050, 1035, 980-955, 880-800; PMR($CDCl_3$) of acetyl derivative: $\delta$ 0.70 (*d*, 3H, sec. $CH_3$), 0.76 (*s*, 6H, 2 × $CH_3$ sec.), 0.81 (*m*, 3H, primary $CH_3$), 0.94 (*s*, 3H, tert. $CH_3$), 1.20-2.00 (complex *m*, 27, methylene protons), 2.02 (*s*, 3H, OAc at C-3), 5.50 (*dd*, 1H, vinylic H); MS: *m/z* 410 ($M^+$), 395, 392, 381, 314, 300, 271, 234, 216, 202. The genin was identified as; stigmasta-7,16,25(26)-trien-3$\beta$-ol by its fragmentation pattern, m.m.p. determination and co-TLC with an authentic sample.

Periodate oxidation[9], partial and enzymatic hydrolysis[10] along with permethylation[11] studies indicated the saponin to contain one molecule each of D-xylose and D-glucose and that D-glucose was present in pyranose form while D-xylose in furanose form. It also indicated that D-xylose unit was attached to sapogenin while D-glucose was the terminal sugar and that all the glycosidic linkages were of $\beta$ type.

The fruits (2 kg) of *Cucumis momordica*, supplied by M/s United Chemical and Allied Product, Calcutta and authenticated by Botany Department of this University, were air dried, crushed and extracted with 95% ethanol. The extract was concentrated to a dirty green viscous mass which was successively extracted with benzene, chloroform, ethyl acetate, acetone and methanol. The methanol soluble fraction on concentration gave a dirty green viscous mass which on addition of excess of solvent ether gave a precipitate. The latter was subjected to purification by column chromatography using silica gel G. The acetone-methanol eluate yielded the saponin (0.06%).

The authors are grateful to CDRI, Lucknow for spectral data. One of them (PC) is thankful to BPRD, New Delhi for financial assistance.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 801-802

# Chemical Investigation of *Macaranga indica* Wight

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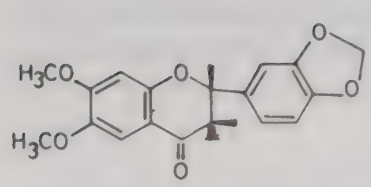
*Received* 13 *October* 1986; *accepted* 18 *December* 1986

A new flavanone, 6,7-dimethoxy-3′,4′-methylenedioxyflavanone (I), sumatrol (II) and 7-methyltectorigenin (III), have been isolated from the acetone extract of the leaves of *Macaranga indica* Wight.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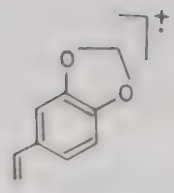
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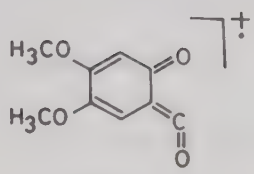
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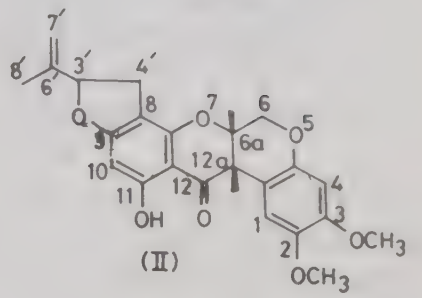
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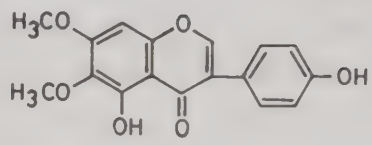
(III)

In our earlier communication[1], the isolation and characterisation of two new prenylated flavanoids were reported from the leaves of *Macaranga indica.* We have isolated from this species a new flavanone, 6,7-dimethoxy-3′,4′-methylenedioxyflavanone (I) along with sumatrol (II) and 7-methyltectorigenin (III).

The plant leaves were collected from Andaman-Nicobar islands. The acetone extract of the leaves on preparative TLC using benzene-pyridine-formic acid (36:9:5) solvent system afforded the compounds I-III.

The compound I crystallised from petrol-benzene as white shinning needles, m.p. 178-79°, $[\alpha]_D$ − 54°. It analysed for $C_{18}H_{16}O_6$ ($M^+$ at *m/z* 328); UV (EtOH): 276 and 34 nm; IR: 1685 $cm^{-1}$($\nu$ C=O). It gave blue colour with Mg/HCl and orange red colour with conc $H_2SO_4$. The presence of a two-proton multiplet at δ 2.57 and a one-proton multiplet at 5.45 in the PMR spectrum of I in $CDCl_3$ + DMSO-$d_6$ clearly characterised I as a flavanone[3]. PMR spectrum of I further displayed two one-proton singlets at δ 7.42 and 6.6 assignable to 5-H and 8-H respectively[4]. A six-proton singlet at δ 3.95 could be due to two $OCH_3$ groups. A singlet at δ 6.18 for a methylenedioxy group was also observed. A three-proton multiplet centred at δ 7.04, analysed as one doublet (J ≃ 10 Hz), one *dd* (J ≃ 10, 3 Hz) and one doublet (*J* ≃ 3 Hz) could be attributed to 2′,5′ and 6′-protons[5].

The mass spectrum of the flavanone showed the molecular ion peak at *m/z* 328 (68%). The base peak at *m/z* 48 and a strong peak at *m/z* 180 could be ascribed to ions (IV) and (V) formed by the retro-dene cleavage of the flavanone nucleus[5].

The structure (I) was further supported by $^{13}C$ NMR spectrum which exhibited signals at δ 191.0 (*s*, *C*=O), 44.3 (*t*, C-3), 80.3 (*d*, C-2) and 101.5 (*t*-methylenedioxy carbon). The signals at δ 100.5, 106.9, 107.6, 108.6, 120.3 and 132 could be assigned to C-8, C-2′, C-5, C-5′, C-6′ and C-1′ respectively. The two methoxyl carbons appeared at δ 56.4. The remaining six signals at δ 106.9, 148.6, 148.0, 190.81, 151.4 and 113.4 were assigned to carbons 2′, 3′, 4′, 4, 9 and 10.

Compound II crystallised from acetone as colourless needles, m.p. 190-92°. It analysed for $C_{23}H_{22}O_7$ and contained two methoxyl groups. It gave a deep brown colouration of tinged green with alc. $FeCl_3$. A purple colouration in Durham test[6] and a green one in Rogers and Calamari test[7] indicated it to be a rotenoid; UV (EtOH): 257, 275, 305 and 335 nm; IR: 1686, 1631, 1587, 1549, 1504 and 937 $cm^{-1}$. On dehydrogenation II gave a colourless optically active compound, identified (m.p., m.m.p.) as dehydrosumatrol by direct comparison with an authentic sample. The carbon-13 NMR spectrum of sumatrol was also compatible with its structure. Thus compound II was established as sumatrol.

Compound III crystallised from MeOH as yellow needles, m.p. 235-36°. It analysed for $C_{17}H_{14}O_6$ ($M^+$ 314); UV (EtOH): 268, 334 (inflection); + $AlCl_3$: 280 nm; IR (nujol): 3450 (OH), 1645 (C=O), 1605, 1580, 1515, 1495 $cm^{-1}$. The PMR spectrum of III exhibited a one-proton singlet at δ 7.8 due to $C_2$-H, two singlet of three protons each at 3.92 and 3.96 due to methyl protons, a one-proton singlet at 6.46 due to $C_5$-H, and doublets of two pro-

tons each at 6.9 ($J$=9 Hz) and 7.4 ($J$=9 Hz) assignable to 2′, 6′ and 3′, 5′ protons respectively. Its mass spectrum showed peaks at *m/z* 314 ($M^+$, 100%), 299 (M—15, 50%) (corresponding to the loss of methyl) and at 118 due to *p*-hydroxyphenylacetylene ion. Thus the compound III is characterised as 7-methyltectorigenin.

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Indian Journal of Chemistry
Vol. 26B, August 1987, pp. 803-807

# Studies on 4-Thiazolidinone: Part IV—Synthesis & Antimicrobial Activity of *p,p'*-Bis(5-methyl/carboxymethyl-4-oxo-2-phenylthiazolidin-3-ylamidomethylamino)-diphenylsulphones

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*Received* 30 *September* 1986; *revised and accepted* 1 *December* 1986

Some new dapsone derivatives have been prepared bearing a 4-thiazolidinone ring system and their structures established by IR and PMR data. All the compounds show moderate antimicrobial activity.

Several derivatives of aminosulphones have been shown to possess strong tuberculostatic[1,2], antileprotic[3,4] and anticonvulsant[5] activities. 4-Thiazolidinones are also associated with various kinds of biological activities such as hypnotic[6], anaesthetic[7], antifungal[8], analgesic[9], antiviral[10], antithyroid[11], antiphlogistic[12], spinal anaesthetic[13], anticonvulsant[7] and CNS stimulant[14], etc. With a view to getting more active products, we have prepared some diarylsulphones of the type I (**22-63**, Table 2) by the action of thiolactic acid and thiomallic acid on schiff bases (**1-21**, Table 1) obtained from *p,p'*-bis(hydrazinocarbonylmethylamino)diphenylsulphone and different aromatic aldehydes. The structural assignments of the products were based on their IR and PMR spectra. The products were screened for their antimicrobial activity.

*Antimicrobial activity*

4-Thiazolidinone derivatives were screened for their antibacterial and antifungal activities using Cup-Plate method[15]. The testing was carried out at a concentration of 100 $\mu$g/ml using the gram-positive bacteria *Staphylococcous aureus* and *Staphylococcus citrus* and the gram-negative bacteria *Escherichia coli and Salmonella typhosa*. The antifungal testing was carried out against *Aspergillus niger* and *Neurospora cressa*.

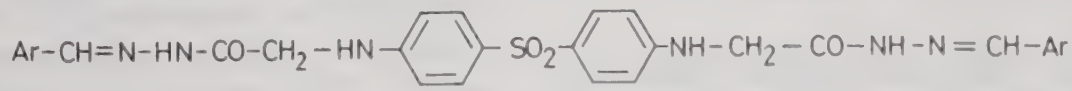
The activity was determined by measuring the zone of inhibition in mm. Known antibiotics available in the market were also tested for their antimicrobial activity. Chloromycetin showed a zone of inhibition of 30 to 35 mm, streptomycein 20 to 25 mm and penicillin G 20 to 23 mm against the various strains of bacteria and fungi using 100 $\mu$g as a test solution.

Most of the compounds showed moderate activity (**14-19** mm, zone of inhibition). The most active compounds among **1-21** (Table 1) were those bearing R = 4-hydroxyphenyl (**20-24** mm), 3-chlorophenyl (**19-22** mm), 3-aminophenyl (**20-23** mm), 4-chlorophenyl (**19-20** mm), 2-hydroxyphenyl (**19-20** mm), 3,4-dimethoxyphenyl (**20-25** mm), 4'-pyridyl (**20-23** mm), 4-nitrophenyl (**20-21** mm), 4-aminophenyl, (**19-22** mm), or 4-hydroxy-3-methoxyphenyl (**19-25** mm).

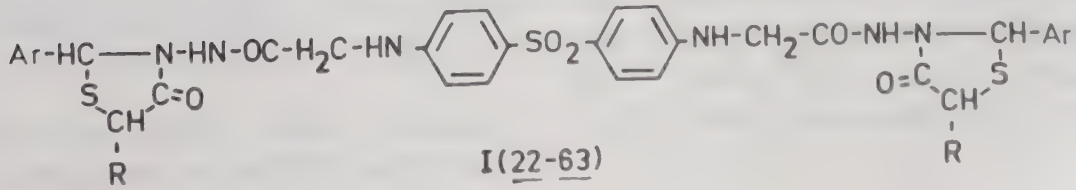
The most active compounds among the *p,p'*-bis(5-methyl-4-oxo-2-phenylthiazolidin-3-ylamidomethylamino)diphenylsulphones (**22-42**) were those bearing R = phenyl (21-23 mm), 4-hydroxyphenyl (19-20 mm), 2-hydroxy-3-methoxyphenyl (19-21 mm), 3,5-dichloro-2-hydroxyphenyl (19-20 mm), 4-tolyl (20-22 mm), 2-hydroxy-1-naphthyl (19-21 mm) or 3-nitrophenyl (19-24 mm).

In the case of *p,p'*-bis(5-carboxymethyl-4-oxo-2-phenylthiazolidin-3-ylamidomethylamino)diphenylsulphones (**43-63**) maximum activity was shown by those members bearing R = 2,4-dichlorophenyl (19-20 mm), 3-aminophenyl (19-21 mm), 4-aminophenyl (20-21 mm), 4-tolyl (**21-24** mm), 4-nitrophenyl (**19-21** mm), 3-hydroxy-4-methoxyphenyl (**19-20** mm), 2-hydroxyphenyl (**20-22** mm), 4-dimethylaminophenyl (**19-22** mm) or 3,5-dichloro-2-hydroxyphenyl (**19-24** mm).

Melting points reported are uncorrected. IR spectra ($\nu_{max}$ in $cm^{-1}$) were recorded in KBr on a Shimadzu infrared spectrophotometer model 435, PMR spectra




(1-21)




I(22-63)

Table 1 — Physical Data of *p,p'*-Bis(substituted benzalhydrazinocarbonylmethylamino)diphenylsulphones (**1-21**)

| Compd | Ar | m.p. °C | Yield (%) | Mol. formula | Found (%) (Calc.) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| **1** | Phenyl | 185 | 81 | $C_{30}H_{28}O_4N_6S$ | 63.4 (63.5 | 4.8 4.9 | 14.8 14.8) |
| **2** | 2-Hydroxyphenyl | 220 | 73 | $C_{30}H_{28}O_6N_6S$ | 60.0 (60.0 | 4.6 4.6 | 14.0 14.0) |
| **3** | 4-Hydroxyphenyl | 205 | 70 | $C_{30}H_{28}O_6N_6S$ | 60.1 (60.1 | 4.7 4.8 | 13.9 14.0) |
| **4** | 2-Hydroxy-1-naphthyl | 220 | 62 | $C_{38}H_{32}O_6N_6S$ | 65.1 (65.1 | 4.7 4.8 | 11.9 12.0) |
| **5** | 2-Hydroxy-3-methoxyphenyl | 124 | 69 | $C_{32}H_{32}O_8N_6S$ | 58.0 (58.1 | 4.8 4.9 | 12.7 12.7) |
| **6** | 3-Hydroxy-4-methoxyphenyl | 116 | 54 | $C_{32}H_{32}O_8N_6S$ | 58.1 (58.1 | 4.9 4.9 | 12.7 12.7) |
| **7** | 4-Hydroxy-3-methoxyphenyl | 210 | 50 | $C_{32}H_{32}O_8N_6S$ | 58.2 (58.3 | 4.8 4.9 | 12.7 12.7) |
| **8** | 3-Aminophenyl | 270 | 87 | $C_{30}H_{30}O_4N_8S$ | 60.1 (60.2 | 5.0 5.0 | 18.7 18.7) |
| **9** | 4-Aminophenyl | 242 | 86 | $C_{30}H_{30}O_4N_8S$ | 60.2 (64.3 | 5.2 5.3 | 18.6 18.7) |
| **10** | Tolyl | 121 | 79 | $C_{32}H_{32}O_4N_6S$ | 64.3 (64.4 | 5.3 5.4 | 13.9 13.9) |
| **11** | 4-Anisyl | 126 | 83 | $C_{32}H_{32}O_6N_6S$ | 61.0 (61.1 | 5.0 5.1 | 13.4 13.4) |
| **12** | 3-Nitrophenyl | 211 | 55 | $C_{30}H_{26}O_8N_8S$ | 54.6 (54.7 | 5.1 5.1 | 17.0 17.0) |
| **13** | 4-Nitrophenyl | 195 | 62 | $C_{30}H_{26}O_8N_8S$ | 54.6 (54.7 | 5.0 5.1 | 17.0 17.0) |
| **14** | 2-Chlorophenyl | 174 | 72 | $C_{30}H_{26}O_4N_6SCl_2$ | 56.5 (56.5 | 4.1 4.1 | 13.2 13.2) |
| **15** | 4-Chlorophenyl | 178 | 81 | $C_{30}H_{26}O_4N_6SCl_2$ | 56.4 (56.5 | 4.0 4.1 | 13.1 13.2) |
| **16** | 2,4-Dichlorophenyl | 218 | 64 | $C_{30}H_{24}O_4N_6SCl_4$ | 51.0 (51.0 | 3.3 3.3 | 11.9 11.9) |
| **17** | 3,5-Dichloro-2-hydroxyphenyl | 180 | 62 | $C_{30}H_{24}O_6N_6SCl_4$ | 48.8 (48.8 | 3.0 3.2 | 11.4 11.4) |
| **18** | 4-Dimethylaminophenyl | 173 | 70 | $C_{34}H_{38}O_4N_8S$ | 62.3 (62.4 | 5.7 5.8 | 7.1 7.1) |
| **19** | 3,4-Dimethylaminophenyl | 190 | 63 | $C_{34}H_{36}O_8N_8S$ | 56.9 (57.0 | 5.0 5.0 | 12.2 12.2) |
| **20** | 4'-Pyridyl | 182 | 58 | $C_{30}H_{28}O_8N_8S$ | 54.4 (54.5 | 4.3 4.5 | 17.8 17.8) |
| **21** | Cinnamyl | 230 | 73 | $C_{34}H_{32}O_4N_6S$ | 65.7 (65.8 | 5.1 5.2 | 13.5 13.5) |

in DMSO-$d_6$ on a EM-360 60 MHz spectrometer using TMS as internal standard (chemical shifts in $\tau$, ppm).

*p,p'-Bis(hydrazinocarbonylmethylamino)-diphenylsulphone*

A mixture of *p,p'*-bis(carbmethoxymethylamino)diphenylsulphone (0.01 mol), ethanol (95%; 30 ml) and hydrazine hydrate (100%; 0.02 mol) was refluxed for 36 hr, ethanol removed and the product isolated and crystallised from DMF, m.p. 98°, yield 83%; IR(KBr): 3450, 3350, 3280, 1675, 1375 and 1150 (Found: C, 49.0; H, 5.1; N, 21.4. $C_{16}H_{20}O_4N_6S$ requires C, 49.0; H, 5.1; N, 21.4%).

*p,p'-Bis(benzalhydrazinocarbonylmethylamino)-diphenylsulphone* (**1**)

A mixture of *p,p'*-bis(hvdrazinocarbonylmethylamino)diphenylsulphone (0.01 mol) and benzaldehyde (0.02 mol) was refluxed in an oil-bath at 110° for 5 hr. The product was isolated and crystallised from DMF, m.p. 185°, yield 81%; IR (KBr): 3250, 1670, 1600, 1520, 1370, 1300 (Found: C, 63.4; H, 4.9; N, 14.7. $C_{30}H_{28}O_4N_6S$ requires C, 63.4; H, 4.9; N, 14.8%).

Similarly other schiff bases (**2-21**) were prepared. Their physical data are recorded in Table 1.

Table 2—Physical Data of *p,p'*-Bis(5-methyl/carboxymethyl-4-oxo-2-phenylthiazolidin-3-ylamidomethylamino)-diphenylsulphones (**22-63**)

| Compd | Ar | m.p. °C | Yield (%) | Mol. formula | Found (%) (Calc.) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| | | | R = $CH_3$ | | | | |
| **22** | Phenyl | 212 | 72 | $C_{36}H_{36}O_6N_6S_3$ | 58.0 (58.1) | 4.7 4.8 | 11.1 11.2) |
| **23** | 2-Hydroxyphenyl | 238 | 80 | $C_{36}H_{36}O_8N_6S_3$ | 55.6 (55.7 | 4.5 4.7 | 10.7 10.8) |
| **24** | 4-Hydroxyphenyl | 183 | 72 | $C_{36}H_{36}O_8N_6S_3$ | 55.6 (55.7 | 4.4 4.6 | 10.7 10.8) |
| **25** | 2-Hydroxy-1-naphthyl | 212 | 68 | $C_{44}H_{40}O_8N_6S_3$ | 62.5 (62.5 | 4.5 4.7 | 9.6 9.6) |
| **26** | 2-Hydroxy-3-methoxyphenyl | 194 | 66 | $C_{38}H_{40}O_{10}N_6S_3$ | 54.3 (54.5 | 4.7 4.8 | 10.0 10.1) |
| **27** | 3-Hydroxy-4-methoxyphenyl | 200 | 75 | $C_{38}H_{40}O_{10}N_6S_3$ | 54.4 (54.5 | 4.7 4.8 | 10.0 10.1) |
| **28** | 4-Hydroxy-3-methoxyphenyl | 260 | 71 | $C_{38}H_{40}O_{10}N_6S_3$ | 54.3 (54.5 | 4.8 4.8 | 10.0 10.1) |
| **29** | 3-Aminophenyl | 276 | 54 | $C_{36}H_{38}O_6N_8S_3$ | 55.7 (55.8 | 4.9 4.9 | 14.7 14.7) |
| **30** | 4-Aminophenyl | 281 | 50 | $C_{36}H_{38}O_6N_8S_3$ | 55.8 (55.8 | 4.7 4.9 | 14.7 14.7) |
| **31** | 4-Tolyl | 182 | 69 | $C_{38}H_{40}O_6N_6S_3$ | 59.0 (59.0 | 5.1 5.2 | 9.7 9.7) |
| **32** | 4-Anisyl | 221 | 58 | $C_{38}H_{36}O_8N_6S_3$ | 57.0 (57.0 | 4.4 4.5 | 10.6 10.7) |
| **33** | 3-Nitrophenyl | 153 | 72 | $C_{36}H_{34}O_{10}N_8S_3$ | 51.6 (51.8 | 4.0 4.1 | 13.4 13.4) |
| **34** | 4-Nitrophenyl | 212 | 70 | $C_{36}H_{34}O_{10}N_8S_3$ | 51.7 (51.8 | 4.0 4.1 | 13.4 13.4) |
| **35** | 2-Chlorophenyl | 142 | 63 | $C_{36}H_{34}O_6N_6S_3Cl_2$ | 53.0 (53.1 | 4.1 4.2 | 10.3 10.3) |
| **36** | 4-Chlorophenyl | 206 | 71 | $C_{36}H_{34}O_6N_6S_3Cl_2$ | 53.0 (53.1 | 4.2 4.2 | 10.3 10.3) |
| **37** | 2,4-Dichlorophenyl | 232 | 69 | $C_{36}H_{32}O_6N_6S_3Cl_4$ | 49.0 (49.0 | 3.6 3.6 | 13.9 13.9) |
| **38** | 3,5-Dichloro-2-hydroxyphenyl | 216 | 71 | $C_{38}H_{40}O_{10}N_6S_3Cl_4$ | 46.5 (46.6 | 4.0 4.1 | 8.5 8.6) |
| **39** | 4-Dimethylaminophenyl | 210 | 60 | $C_{40}H_{46}O_6N_8S_3$ | 57.6 (57.8 | 5.3 5.5 | 13.1 13.1) |
| **40** | 3,4-Dimethoxyphenyl | 210 | 73 | $C_{40}H_{44}O_{10}N_6S_3$ | 55.4 (55.5 | 5.0 5.1 | 10.0 10.0) |
| **41** | 4'-Pyridyl | 200 | 73 | $C_{36}H_{36}O_8N_8S_3$ | 53.7 (53.7 | 4.5 4.5 | 9.7 9.7) |
| **42** | Cinnamyl | 212 | 80 | $C_{40}H_{40}O_6N_6S_3$ | 60.2 (60.3 | 4.4 4.5 | 10.3 10.6) |
| | | | R = $-CH_2COOH$ | | | | |
| **43** | Phenyl | 112 | 90 | $C_{38}H_{36}O_{10}N_6S_3$ | 54.7 (54.8 | 4.2 4.3 | 10.0 10.1) |
| **44** | 2-Hydroxyphenyl | 210 | 63 | $C_{38}H_{36}O_{12}N_6S_3$ | 52.6 (52.8 | 4.0 4.2 | 9.6 9.7) |
| **45** | 4-Hydroxyphenyl | 260 | 53 | $C_{38}H_{36}O_{12}N_6S_3$ | 52.7 (52.8 | 4.1 4.2 | 9.7 9.7) |
| **46** | 2-Hydroxy-1-naphthyl | 240 | 45 | $C_{46}H_{40}O_{12}N_6S_3$ | 57.1 (57.2 | 4.1 4.1 | 8.7 8.7) |
| **47** | 2-Hydroxy-3-methoxyphenyl | 230 | 68 | $C_{40}H_{36}O_{14}N_6S_3$ | 52.1 (52.2 | 3.8 3.9 | 9.1 9.1) |
| **48** | 3-Hydroxy-4-methoxyphenyl | 270 | 72 | $C_{40}H_{36}O_{14}N_6S_3$ | 52.0 (52.2 | 3.9 3.9 | 9.1 9.1) |

Table 2—Physical Data of *p,p'*-Bis(5-methyl/carboxymethyl-4-oxo-2-phenylthiazolidin-3-ylamidomethylamino)-diphenylsulphones (**22-63**)—(*Contd.*)

| Compd | Ar | m.p., °C | Yield (%) | Mol. formula | Found (%) (Calc.) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| **49** | 4-Hydroxy-3-methoxyphenyl | 195 | 70 | $C_{40}H_{36}O_{14}N_6S_3$ | 52.2 (52.2 | 3.8 3.9 | 9.1 9.1) |
| **50** | 3-Aminophenyl | 230 | 66 | $C_{38}H_{38}O_{10}N_8S_3$ | 52.9 (52.9 | 4.3 4.4 | 12.9 13.0) |
| **51** | 4-Aminophenyl | 236 | 55 | $C_{38}H_{38}O_{10}N_8S_3$ | 52.8 (52.9 | 4.3 4.4 | 12.9 13.0) |
| **52** | 4-Tolyl | 330 | 42 | $C_{40}H_{40}O_{10}N_6S_3$ | 55.7 (55.8 | 4.6 4.7 | 9.7 9.7) |
| **53** | 4-Anisyl | 270 | 56 | $C_{40}H_{36}O_{12}N_6S_3$ | 54.0 (54.0 | 4.0 4.0 | 9.4 9.5) |
| **54** | 3-Nitrophenyl | 108 | 61 | $C_{38}H_{36}O_{14}N_8S_3$ | 49.2 (49.3 | 3.8 3.9 | 12.1 12.1) |
| **55** | 4-Nitrophenyl | 224 | 38 | $C_{38}H_{36}O_{14}N_8S_3$ | 49.2 (49.3 | 3.8 3.9 | 12.1 12.1) |
| **56** | 2-Chlorophenyl | 230 | 52 | $C_{38}H_{34}O_{10}N_6S_3Cl_2$ | 50.5 (50.6 | 3.7 3.8 | 9.3 9.3) |
| **57** | 4-Chlorophenyl | 145 | 58 | $C_{38}H_{34}O_{10}N_6S_3Cl_2$ | 50.4 (50.6 | 3.8 3.8 | 9.3 9.3) |
| **58** | 2,4-Dichlorophenyl | 260 | 38 | $C_{38}H_{32}O_{10}N_6S_3Cl_4$ | 47.0 (47.0 | 3.2 3.3 | 8.9 9.0) |
| **59** | 3,5-Dichloro-2-hydroxyphenyl | 185 | 48 | $C_{38}H_{32}O_{12}N_6S_3Cl_4$ | 45.4 (45.5 | 3.1 3.2 | 8.3 8.4) |
| **60** | 4-Dimethylaminophenyl | 183 | 62 | $C_{42}H_{46}O_{10}N_8S_3$ | 54.7 (54.9 | 5.0 5.0 | 9.4 9.4) |
| **61** | 3,4-Dimethoxyphenyl | 152 | 58 | $C_{42}H_{44}O_{14}N_6S_3$ | 52.8 (52.9 | 4.4 4.6 | 8.7 8.8) |
| **62** | 4'-Pyridyl | 125 | 70 | $C_{38}H_{36}O_{12}N_8S_3$ | 51.0 (51.1 | 4.0 4.0 | 12.4 12.5) |
| **63** | Cinnamyl | 220 | 75 | $C_{42}H_{40}O_{10}N_6S_3$ | 57.0 (57.0 | 4.4 4.5 | 9.4 9.5) |

*p,p'-Bis(5-methyl-4-oxo-2-phenylthiazolidin-3-ylamidomethylamino)diphenylsulphone* (**22**)

Thiolactic acid (0.02 mol) was added to *p,p'*-bis(benzalhydrazinocarbonylmethylamino)diphenylsulphone (0.01 mol), and the reaction mixture refluxed in an oil-bath at 120° for 6 hr. The product was isolated and crystallised from methanol, m.p. 212°, yield 72%; IR(KBr): 3360, 3080, 1685, 1670, 1350, 1300, 1150; PMR(DMSO-$d_6$): 2.2-3.1 (*m*, 18H, Ar − *H*), 6.2 (*s*, 2H, $-CH_2CO$), 6.1 (*q*, 1H, R − CHCO of thiazolidinone), 7.6 (*s*, 1H, −S−CH−R of thiazolidinone), 9.05 (*d*, 3H, $CH_3-CHCO$ of thiazolidinone (Found: C, 58.0; H, 4.8; N, 11.2. $C_{36}H_{36}O_6N_6S_3$ requires C, 58.1; H, 4.3; N, 11.3%).

Similarly, other 4-thiazolidinone (**23-42**) were prepared. Their physical data are recorded in Table 2.

*p,p'-Bis(5-carboxymethyl-4-oxo-2-phenylthiazolidin-3-ylamidomethylamino)diphenylsulphone* (**43**)

A mixture of thiomallic acid (0.02 mol), benzaldehyde (0.02 mol) and *p,p'*-bis(hydrazinocarbonylmethylamino)diphenylsulphone (0.01 mol) was heated in an oil-bath at 160° for 2 hr. The product was dissolved in aq. NaOH solution (1%; 30 ml) and filtered. The filtrate was treated with dil. hydrochloric acid and the precipitated product crystallised from acetic acid, m.p. 112°, yield 93%; IR(KBr): 3550, 3350, 3050, 1720, 1680, 1650, 1600, 1360, 1170; PMR(DMSO-$D_6$): 2.2 to 3.1 (*m*, 18H, Ar − *H*), 6.15 (*s*, 2H, $-CH_2CO$), 7.3 (*t*, 1H, *R'* − CHCO of thiazolidinone), 7.5 (*s*, 1H, −S−CH−R of thiazolidinone), 9.0 (*d*, 2H, $HOOC-CH_2-\underset{1}{CH}-CO-$ of thiazolidinone) (Found: C, 54.8; H, 4.3; N, 10.0. $C_{38}H_{36}O_{10}N_6N_6S_3$ requires C, 54.8; H, 4.3; N, 10.0.

Similarly, other 4-thiazolidinones (**44-63**) were prepared. Their physical data are recorded in Table 2.

The authors are thankful to Prof. A R Parikh for providing research facilities and to the Ministry of Higher Education, Government of Iran, Tehran for research scholarship to two of us (M A S & M H M).

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Indian Journal of Chemistry
Vol. 26B, August 1987, p. 808

# ANNOUNCEMENTS

## IUPAC Recommendations on the Nomenclature of Steroids (Recommendations 1986)

The recommendations on nomenclature of steroids have a long history; the most recent recommendations were published in *Pure Appl Chem*, **31** (1972) 285-322, and elsewhere. Since then, many of the principles developed for naming steroids have been generally adopted and have become part of the IUPAC *Nomenclature of Organic Chemistry* (Pergamon Press, Oxford 1979), in Section F (Natural Products). The present decument is a revision of the earlier recommendations made necessary in the light of new developments and current practice.

The main changes are as follows: (i) modifications, where appropriate to conform to Section F; (ii) incorporation of the new recommendations (1981) for the nomenclature of vitamin D [*Pure Appl Chem*, **54** (1982) 1511-1516 and elsewhere]; (iii) wider use of the *R,S*-system for designating the stereochemistry in the side chain; (iv) provision of numbers for alkyl substituents; (v) procedure to fuse additional rings to the steroid; (vi) selection of homo or nor with the appropriate parent; (vii) selected International Non-Proprietary Names (INNs) for steroids; and (viii) the omission of most steroid alkaloid and steroid-like triterpenoids, as it is intended that they should be treated in an appendix to Section F.

Comments should be sent before 31 January 1988 to the Secretary of IUPAC-IUB Joint Commission on Biochemical Nomenclature, Dr A. Cornish-Bowden, CNRS-CBH, BP 71, 31 chemin Josph-Aiguier, F-13402 Marseille Cedex 9, France.

Those desirous of having full texts of the above recommendations may write to the Executive Secretary, Indian National Science Academy, Bahadur Shah Zafar Marg, New Delhi 110 002.

## 32nd IUPAC Congress 1989

32nd IUPAC Congress, being organised by The Swedish National Committee for Chemistry and the Royal Swedish Academy of Sciences, will be held in Stockholm, Sweden, during 2-7 August 1989.

The scientific programme will be mainly devoted to seven areas of chemistry with plenary and key note addresses by eminent chemists invited from all over the world. The areas to be covered are: (1) large scale separation of biological macromolecules, cells and particles; (2) atmospheric and marine chemistry; (3) chemical communication and interaction between organisms; (4) solid state chemistry — frontiers in the chemistry of inorganic materials; (5) structure and dynamics of macromolecules; (6) electron transfer reactions; and (7) chemistry and biochemistry of bile acids. Although these are the main themes, participants are invited to contribute papers in other areas of chemistry as well.

The first circular, which is now available, can be had from IUPAC, C/o Stockholm Convention Bureau, P.O. Box 6911, S-102, 39 Stockholm, Sweden. Details regarding submission of papers will be given in the second circular to be issued during April, 1988.

## Seminar on Data Storage, Retrieval & Dissemination

A regional (South Asian) seminar-cum-workshop on "Data storage, retrieval and dissemination in science, with special reference to chemical and molecular biosciences" is being organised by the Natio Information Centre for Crystallography (NICRYS) in Madras during 18-23 January 1988. The purpose of the seminar is to focus attention on the scope of modern informatics involving data storage, retrie... and dissemination and the role they play in improving the quality and grade of scientific research, particularly in chemical and molecular biosciences.

For details, queries may be addressed to Prof. R Srinivasan, Honorary Director, NICRYS, Department of Crystallography and Biophysics, University of Madras, Madras 600 025.

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